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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM P.L.C. [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: TEW, David, Graham [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). HICKEY, Deirdre, Mary, Bernadette [IE/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB).

(74) Agent: CONNELL, Anthony, Christopher; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

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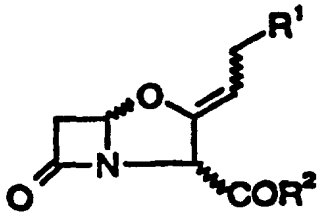
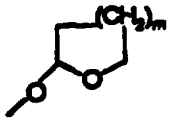
(54) Title: CLAVULANIC ACID DERIVATIVES FOR TREATING ATHEROSCLEROSIS

(57) Abstract



(I)



(a)

Clavulanic acid derivatives of structure (I) in which R^1 is OH, $OCOR^3$, OCHO, $O(CH_2)_nOR^5$, OC_{1-12}alkyl, $O(CH_2)_nCO_2R^5$, $-S(O)_pC_{1-12}$alkyl, $S(CH_2)_qPh$, $S(O)_r(CH_2)_nPh$, N_3, NR^6R^7 or (a); R^2 is $O(CH_2)_nPh$ in which the phenyl ring may optionally be substituted, $O(CH_2)_n$naphthyl, $O(CH_2)_nCOPh$, $O(CH_2)_nSPh$, $OCH(Ph)C_{1-6}$alkyl, OC_{1-6}alkyl, $NR^{10}(CH_2)_qPh$, $NR^{10}(CH_2)_nCOPh$, $N(R^8)O(CH_2)_nPh$; R^3 is C_{1-12}alkyl, C_{2-12}alkenyl, optionally substituted phenyl, $CH(Ph)_2$, biphenyl, $(CH_2)_nPh$, $(CH_2)_n$Het, $(CH_2)_nCO_2R^8$, $(CH_2)_nC_{3-6}$cycloalkyl, $C(R^9)_3$, adamantyl, naphthyl, C_{3-6}cyclohexyl, $(CH_2)_nPh(CH_2)_nPh$ or PhOPh; R^5 is hydrogen or C_{1-6}alkyl; one of R^6 and R^7 is hydrogen or C_{1-6}alkyl, and the other is CHO, CH_2Ph, COC_{1-6}alkyl, COPh, $COCH_2NHCOC_{1-6}$alkyl or $NHCOOCH_2Ph$; R^8 is hydrogen or C_{1-6}alkyl; R^9 is hydrogen or halogen; R^{10} is hydrogen, hydroxy, C_{1-6}alkyl or $OCOCH_3$; m is 1 or 2; n is 1 to 8; p is 0, 1 or 2; q is 0 to 6 and r is 0, 1 or 2; and salts, hydrates and solvates thereof are inhibitors of Lp PLA2 and of use in therapy, in particular for treating atherosclerosis.

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CLAVULANIC ACID DERIVATIVES FOR TREATING ATHEROSCLEROSIS

The present invention relates to certain novel clavulanic acid derivatives, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy, in particular in the treatment of atherosclerosis.

The sequence of the enzyme Lipoprotein Associated Phospholipase A_2 (Lp-PLA_2), the isolation and purification thereof, isolated nucleic acids encoding the enzyme, recombinant host cells transformed with DNA encoding the enzyme are described in patent application WO 95/00649 (SmithKline Beecham plc). Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A later patent application (WO 95/09921, Icos Corporation) and a related publication in Nature (Tjoelker et al, vol 374, 6 April 1995, 549) describe the same enzyme, although calling it by the name 'Platelet Activating Factor Acetyl Hydrolase' (PAF acetyl hydrolase) and suggest that it may have potential as a therapuetic protein for regulating pathological inflammatory events.

Lp-PLA_2 is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-PLA_2 action are biologically active with lysophosphatidylcholine, a component of oxidised LDL, known to be a potent chemoattractant for circulating monocytes. As such, lysophosphatidylcholine is thought play a significant role in atherosclerosis by being responsible for the accumulation of cells loaded with cholesterol ester in the arteries. Inhibition of the Lp-PLA_2 enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-PLA_2 could therefore prove beneficial in the treatment of this phenomenon. A Lp-PLA_2 inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

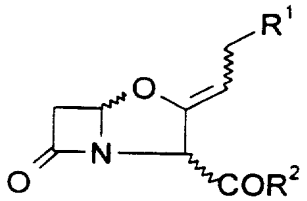
Lp-PLA_2 inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA_2. Examples of such disorders include psoriasis.

Lp-PLA_2 inhibitors may also have a general application in any disorder that involves lipid peroxidation in conjunction with Lp-PLA_2 activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, reperfusion injury, sepsis and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia.

Recently published International patent applications WO 96/13484 and WO 96/19451 (SmithKline Beecham plc) disclose two series of substituted azetidin-2-ones which are inhibitors of Lp PLA_2.

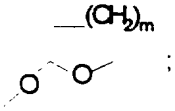
We have now identified a further series of compounds which have been found to act as inhibitors of Lp-PLA_2.

The present invention provides in a first aspect compounds of structure (I):



(I)

in which:

R^1 is OH, OCR^3, OCHO, $O(CH_2)_nOR^5$, OC_{1-12}alkyl, $O(CH_2)_nCO_2R^5$, $-S(O)_pC_{1-12}$alkyl, $S(CH_2)_q$Ph, $S(O)_r(CH_2)_n$Ph, N_3, NR^6R^7 or  ;

R^2 is $O(CH_2)_n$Ph in which the phenyl ring may optionally be substituted, $O(CH_2)_n$naphthyl, $O(CH_2)_nCOPh$, $O(CH_2)_nSPh$, $OCH(Ph)C_{1-6}$alkyl, OC_{1-6}alkyl, $NR^{10}(CH_2)_q$Ph, $NR^{10}(CH_2)_nCOPh$, $N(R^8)O(CH_2)_n$Ph;

R^3 is C_{1-12}alkyl, C_{2-12}alkenyl, optionally substituted phenyl, $CH(Ph)_2$, biphenyl, $(CH_2)_n$Ph, $(CH_2)_n$Het, $(CH_2)_nCO_2R^8$, $(CH_2)_nC_{3-6}$cycloalkyl, $C(R^9)_3$, adamantyl, naphthyl, C_{3-6}cyclohexyl, $(CH_2)_n$Ph$(CH_2)_n$Ph or PhOPh;

R^5 is hydrogen or C_{1-6}alkyl;

one of R^6 and R^7 is hydrogen or C_{1-6}alkyl, and the other is CHO, CH_2Ph, COC_{1-6}alkyl, COPh, $COCH_2NHCOC_{1-6}$alkyl or $NHCOOCH_2Ph$;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is hydrogen or halogen;

R^{10} is hydrogen, hydroxy, C_{1-6}alkyl or $OCOCH_3$;

m is 1 or 2; n is 1 to 8; p is 0, 1 or 2; q is 0 to 6 and r is 0, 1 or 2;

and salts, hydrates and solvates thereof.

Preferably R^1 is OH, $OCOR^3$ or NR^6R^7. Most preferably R^1 is $NHCOCH_3$.

Preferably R^2 is $O(CH_2)_nPh$, in which n is 1 to 8, in particular 6.

Preferably R^3 is C_{1-12}alkyl. Most preferably R^3 is methyl.

Preferably R^5 is hydrogen.

Preferably, one of R^6 and R^7 is hydrogen and the other is COC_{1-6}alkyl, in particular $COCH_3$.

Preferably R^8 is hydrogen.

Preferably one group R^9 is hydrogen and the other two are halogen, in particular chlorine.

Preferably R^{10} is hydrogen.

Preferably, m is 2.

Preferably, n is 6.

Preferably, p is 2.

Preferably, q is 0 to 6. Most preferably q is 0 or 1.

Preferably, r is 0, 1 or 2. Most preferably r is 2.

The term optionally substituted phenyl ring as used herein shall be taken to include phenyl rings substituted by 1 to 3 substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, amino, C_{1-6}alkylthio, halogen, cyano, hydroxy, carbamoyl, carboxy, C_{1-6}alkanoyl or trifluoromethyl. C_{1-6} and C_{1-12}alkyl groups (either alone or as part of another group) can be straight or branched.

Compounds of structure (I) can form salts, in particular pharmaceutically acceptable acid addition salts with suitable organic and inorganic acids the nature of which will be apparent to persons skilled in the art. For example, pharmaceutically acceptable salts can be formed by reaction with hydrochloric, sulphuric, or phosphoric acids; aliphatic, aromatic or heterocyclic sulphonic acids or carboxylic acids such as for example, citric, maleic or fumaric acids.

The compounds of structure (I) can be prepared starting, for example, from potassium clavulanate by processes analogous to those known to those skilled in the art as described in the specific examples hereinafter.

Compounds of the present invention are inhibitors of the enzyme lipoprotein associated phospholipase A_2 (Lp-PLA_2) and as such are expected to be of use in therapy, in particular in the treatment of atherosclerosis. In a further aspect therefore the present invention provides a compound of formula (I) for use in therapy.

The compounds of formula (I) are inhibitors of lysophosphatidylcholine production by Lp-PLA_2 and may therefore also have a general application in any disorder that involves endothelial dysfunction, for example atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion. In addition, compounds of formula (I) may have a general application in any disorder that involves lipid peroxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia.

Further applications include any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA_2. Examples of such disorders include psoriasis.

Accordingly, in a further aspect, the present invention provides for a method of treating a disease state associated with activity of the enzyme Lp-PLA_2 which method involves treating a patient in need thereof with a therapeutically effective amount of an inhibitor of the enzyme. The disease state may be associated with the increased involvement of monocytes, macrophages or lymphocytes; with the formation of lysophosphatidylcholine and oxidised free fatty acids; with lipid peroxidation in conjunction with Lp PLA2 activity; or with endothelial dysfunction.

Compounds of the present invention may also be of use in treating the above mentioned disease states in combination with anti-hyperlipidaemic or anti-atherosclerotic or anti-diabetic or anti-anginal or anti-inflammatory or anti-hypertension agents. Examples of the above include cholesterol synthesis inhibitors such as statins, anti-oxidants such as probucol, insulin sensitisers, calcium channel antagonists, and anti-inflammatory drugs such as NSAIDs.

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

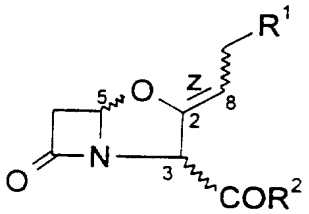
Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

The following examples serve to illustrate the invention.

Unless otherwise stated all compounds have the 3R. 5R. $\Delta_{2,8}Z$ stereochemistry.



Example 1: $R^2 = O(CH_2)_6$-(4- F)Ph. $R^1 = OH$

6-(4-Fluorophenyl)hexyl clavulanate

(a) 6-(4-Fluorophenyl)hexyl bromide

6-Bromohexanoyl chloride (125 g , 0.585mol) was added over 5 minutes to a suspension of aluminium chloride (71.6 g, 0.537mol) in CH_2Cl_2 (1000ml) whilst keeping the temperature at 20-25°C. The mixture was treated with fluorobenzene (46.5 g, 0.484mol) dropwise over 10 minutes. After stirring at room temperature for 19 hours. triethylsilane (139.4 g, 1.2mol) was added over 10 minutes keeping the temperature below 35°C. The mixture was stirred at room temperature for 60 minutes then poured into ice water (1l), extracted with diethyl ether (1.5l). The organic layer was washed with water (x5), brine (x2), dried ($MgSO_4$) and evaporated in vacuo. The residue was distilled under reduced pressure to give a clear oil (111.9 g), boiling point 116-126°C/0.1mbar. Purification by column chromatography on silica gel using hexane as eluant gave the product as a colourless oil (99.8 g, 80%).

(b) 6-(4-Fluorophenyl)hexyl clavulanate.

A mixture of 6-(4-fluorophenyl)hexyl bromide (1.56 g, 6mmol) and potassium clavulanate (0.95 g, 6mmol) in dimethylformamide (DMF. 60ml) was stirred at room temperature for 18 hours. The mixture was evaporated to dryness and partioned between ethyl acetate (100ml) and water (50ml). The organic layer was separated. washed with brine (x2), dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography on silica gel using 2:1 hexane/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (0.7 g, 46%).

Found: C. 63.3; H. 6.4; N. 3.6%

$C_{20}H_{24}FNO_5$ requires: C. 63.7; H. 6.4 ; N, 3.7%

The following compounds. Examples 2-39. were prepared as above using the appropriate benzyl bromide or alkyl bromide or iodide which was commercially available or prepared by the method described above.

Example 2: $R^2 = OCH_3$. $R^1 = OH$

Methyl clavulanate. Yield = 83%. pale yellow oil.
Found: C. 50.5; H. 5.2; N. 6.5%
$C_9H_{11}NO_5$ requires: C. 50.7; H. 5.2; N. 6.6%
Example 3: R^2= OC_6H_{13}, R^1 = OH
n-Hexyl clavulanate. Yield = 68%. yellow oil.
Found: C. 59.2; H. 7.5; N. 5.1%
$C_{14}H_{21}NO_5$ requires: C. 59.4; H. 7.5; N. 4.9%
Example 4: R^2= $OC_{18}H_{37}$, R^1 = OH
n-Octadecyl clavulanate. Yield = 3.5%. cream solid. m.p. 72-74°C.
Found: C. 69.0; H. 10.0; N. 3.3%
$C_{26}H_{45}NO_5$ requires: C. 69.1; H. 10.0; N. 3.1%
Example 5: R^2= OCH_2Ph, R^1 = OH
Benzyl clavulanate. Yield = 70%. Yellow oil.
Found: C. 61.5; H. 5.3; N. 5.0%
$C_{15}H_{15}NO_5(0.2H_20)$ requires: C. 61.5; H. 5.3; N. 4.8%
Example 6: R^2= OCH_2-(4-NO_2)Ph. R^1 = OH
4-Nitrobenzyl clavulanate. Yield = 60%, yellow solid, m.p. 114-115°C.
Found: C, 53.7; H. 4.2; N, 8.3%
$C_{15}H_{14}N_2O_7$ requires: C. 53.9; H. 4.2; N, 8.4%
Example 7: R^2= OCH_2-(4-Cl)Ph, R^1 = OH
4-Chlorobenzyl clavulanate. Yield = 68.7%, colourless solid, m.p. 94°C.
Found: C. 55.8; H. 4.3; N. 4.4; Cl. 10.8%
$C_{15}H_{14}ClNO_5$ requires: C. 55.7; H. 4.4; N. 4.3; Cl. 11.0%
Example 8: R^2= OCH_2-(4-CH3)Ph. R^1 = OH
4-Methylbenzyl clavulanate. Yield = 38%. colourless solid. m.p. 71-75°C.
Found: C. 63.4; H. 5.7; N. 4.6%
$C_{16}H_{17}NO_5$ requires: C. 63.4; H. 5.6; N, 4.6%
Example 9: R^2= OCH_2-(4-Br)Ph, R^1 = OH
4-Bromobenzyl clavulanate. Yield = 56%. colourless solid. m.p.107-108°C.
Found: C. 48.9; H. 3.9; N. 3.9; Br. 22.1%
$C_{15}H_{14}BrNO_5$ requires: C. 48.9; H. 3.8; N. 3.8; Br. 21.7%
Example 10: R^2= OCH_2-(4-OCH_3)Ph. R^1 = OH
4-Methoxybenzyl clavulanate. Yield = 23%. yellow oil.
Found: C. 59.9; H. 5.4; N. 4.3%
$C_{16}H_{17}NO_6$ requires: C. 60.2; H. 5.4; N. 4.4%
Example 11: R^2= OCH_2-(4-$(CH_3)_3$)Ph. R^1 = OH

4-tert-Butylbenzyl clavulanate. Yield = 41%, yellow oil.
Found: C, 66.0; H, 6.8; N, 3.8%
$C_{19}H_{21}NO_5$ requires: C, 66.1; H, 6.7; N, 4.1%

Example 12: R^2= OCH_2-(4-Ph)Ph, R^1 = OH
4-Biphenylmethyl clavulanate. Yield = 63%, yellow oil.
Found: C, 68.4; H, 5.2; N, 4.1%
$C_{21}H_{19}NO_5(0.2H_2O)$ requires: C, 68.3; H, 5.3; N, 3.8%

Example 13: R^2= OCH_2 -1-Naphthyl, R^1 = OH
(1-Naphthyl)methyl clavulanate. Yield = 70%, yellow oil.
Found: C, 66.9; H, 5.1; N, 3.9%
$C_{19}H_{17}NO_5$ requires: C, 67.3, H, 5.1; N, 4.1%

Example 14: R^2= OCH_2-(4-OH, 3,5-di-tert-butyl)Ph, R^1 = OH
3,5-Di-t-butyl-4-hydroxybenzyl clavulanate. Yield = 2.6%, foam.
Found: C, 66.0; H, 7.6; N, 3.4%
$C_{23}H_{31}NO_6$ requires: C, 66.2; H, 7.5; N, 3.4%

Example 15: R^2= OCH_2-(2,4-diCl)Ph, R^1 = OH
2,4-Dichlorobenzyl clavulanate. Yield = 32%, colourless solid, m.p. 73-74°C.
^{1}H NMR-($CDCl_3$) δ 3.09 (d, J=16.7Hz, 1H, 6β-H), δ 3.50 (dd, J=2.6, 16.7Hz, 1H, 6α-H), δ 4.22 (m, 2H, 9,9'-H), δ 4.92 (t, J=7.0Hz, 1H, 8-H), δ 5.10 (d, J=0.96Hz, 1H, 3-H), δ 5.26-5.28 (2xd, J=12.8Hz, 2H, CH_2Ar), δ 5.70 (d, J=2.6Hz, 1H, 5-H), δ 7.29 (m, 2H, Ar-H), δ 7.44 (d, J=2.0Hz, 1H, Ar-H).

Example 16: R^2= OCH_2-(2,6-diCl)Ph, R^1 =OH
2,6-Dichlorobenzyl clavulanate. Yield = 46%, colourless solid, m.p. 111°C.
Found: C, 50.2; H, 3.7; N, 3.9; Cl, 20.0%
$C_{15}H_{13}Cl_2NO_5$ requires: C, 50.3; H, 3.7; N, 3.9; Cl, 19.8%

Example 17: R^2= OCH_2-(2,5-diCl)Ph, R^1 =OH
2,5-Dichlorobenzyl clavulanate. Yield 7.5%, colourless solid, m.p. 110°C.
Found: C, 50.3; H, 3.8; N, 4.0; Cl, 19.5%
$C_{15}H_{13}Cl_2NO_5$ requires: C, 50.3; H, 3.7; N, 3.9; Cl, 19.8 %

Example 18: R^2= OCH_2-(2,4-diCl)Ph, R^1 = OH
2,4-Dichlorobenzyl clavulanate. Yield = 40%, colourless solid, m.p. 61-62°C.
Found: C, 50.3; H, 3.8; N, 3.9%
$C_{15}H_{13}Cl_2NO_5$ requires: C, 50.3; H, 3.7; N, 3.9%

Example 19: R^2= OCH_2-(2,3-diCl)Ph, R^1 = OH
2,3-Dichlorobenzyl clavulanate. Yield = 26%, colourless solid, m.p. 71°C.
Found: C, 50.4; H, 3.8; N, 3.9%

$C_{15}H_{13}Cl_2NO5$ requires: C, 50.3; H, 3.7; N, 3.9%

Example 20: R^2= $O(CH_2)_5CO$-(4-Cl)Ph, R^1 = OH

6-(4-Chlorophenyl)-5-oxo-hexyl clavulanate. Yield = 33%, yellow oil.

Found: C, 58.1; H, 5.5; N, 3.3; Cl, 9.9%

$C_{20}H_{22}ClNO_6(0.08CH_2Cl_2)$ requires: C, 58.2; H, 5.4; N, 3.4; Cl, 9.9%

Example 21: R^2= $OCH(CH_3)$Ph, R^1 = OH

R,S-1-Phenylethyl clavulanate. Yield = 47%, pale yellow oil.

Found: C, 63.1; H, 5.7; N, 4.6%

$C_{16}H_{17}NO_5$ requires: C, 63.4; H, 5.7; N, 4.6%

Example 22: R^2= $O(CH_2)_3$Ph, R^1 = OH

3-Phenylpropyl clavulanate. Yield = 56%, colourless oil.

Found: C, 64.5; H, 6.1; N, 4.6%

$C_{17}H_{19}NO_5$ requires: C, 64.3; H, 6.0; N, 4.4%

Example 23: R^2= $O(CH_2)_8$Ph, R^1 = OH

8-Phenyloctyl clavulanate. Yield = 32%, colourless oil.

Found: C, 68.4; H, 7.5; N, 3.6 %

$C_{22}H_{29}NO_5$ requires: C, 68.2; H, 7.5; N, 3.6%

Example 24: R^2= $O(CH_2)_6$-(4-Br)Ph, R^1 = OH

6-(4-Bromophenyl)hexyl clavulanate. Yield = 43%, yellow oil.

Found: C, 54.8; H, 5.5; N, 3.5; Br, 18.5%

$C_{20}H_{24}BrNO_5$ requires: C, 54.8; H, 5.5; N, 3.2; Br, 18.2%

Example 25: R^2= $O(CH_2)_6$Ph, R^1 = OH

6-Phenylhexyl clavulanate. Yield = 51%, yellow oil.

Found: C, 66.7; H, 7.0; N, 3.9%

$C_{20}H_{25}NO_5$ requires: C, 66.8; H, 7.0; N, 3,9%

Example 26: R^2= $O(CH_2)_6$-(4-Cl)Ph, R^1 = OH

6-(4-Chlorophenyl)hexyl clavulanate. Yield = 39%, yellow oil.

Found; C, 59.4; H, 6.1; N, 3.2%

$C_{20}H_{24}ClNO_5(O.5H_2O)$ requires: C, 59.2; H, 6.2; N, 3.5%

Example 27: R^2= $O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = OH

6-(4-n-Butylphenyl)hexyl clavulanate. Yield = 33%, yellow oil.

Found: C, 68.9; H, 7.9; N, 3.5%

$C_{24}H_{33}NO_5$ requires: C, 69.4; H, 8.0; N, 3.4%

Example 28: R^2= $O(CH_2)_6$-(2,4-diCl)Ph, R^1 = OH

6-(2,4-Dichlorophenyl)hexyl clavulanate. Yield = 30%, yellow oil.

Found: C, 56.0; H, 5.5; N, 3.4; Cl, 16.1%

$C_{20}H_{23}Cl_2NO_5(0.083EtOAc)$ requires: C, 56.1; H, 5.5; N, 3.2; Cl, 16.3%

Example 29: R^2= $O(CH_2)_6$-(2,4-diCH_3)Ph, R^1 = OH

6-(2,4-Dimethylphenyl)hexyl clavulanate. Yield = 23%, yellow oil.

Found: C, 68.2; H, 7.5; N, 3.5%

$C_{22}H_{29}NO_5$ requires: C, 68.2; H, 7.5; N, 3.6%

Example 30: R^2= $O(CH_2)_5$-(2,4-diCl)Ph, R^1 = OH

5-(2,4-Dichlorophenyl)pentyl clavulanate. Yield = 18%, pale yellow solid, m.p. 61-62°C

Found: C, 55.2; H, 5.1; N, 3.4; Cl, 16.7%

$C_{19}H_{21}Cl_2NO_5(0.02C_6H_{14})$ requires: C, 55.2; H, 5.2; N, 3.4; Cl, 17.1%

Example 31: R^2= $O(CH_2)_4$-(4-CH_3)Ph, R^1 = OH

4-(4-Methylphenyl)butyl clavulanate. Yield = 47%, pale yellow oil.

Found: C, 65.8; H, 6.7; N, 3.9%

$C_{19}H_{23}NO_5$ requires: C, 66.1; H, 6.7; N, 4.1%

Example 32: R^2= $O(CH_2)_4$-(4-OCH_3)Ph, R^1 = OH

6-(4-Methoxyphenyl)butyl clavulanate. Yield = 57%, yellow oil.

Found: C, 62.9; H, 6.4; N, 3.7%

$C_{19}H_{23}NO_6$ requires: C, 63.2; H, 6.4; N, 3.9%

Example 33: R^2= $O(CH_2)_4$-(4-Ph)Ph, R^1 = OH

4-(4-Biphenyl)butyl clavulanate. Yield = 56%, colourless solid, m.p. 86-88°C.

Found: C, 70.5; H, 6.2; N, 3.5%

$C_{24}H_{25}NO_5$ requires: C,70.8; H, 6.2; N, 3.4%

Example 34: R^2= $O(CH_2)_6$-(4-OH)Ph, R^1 = OH

6-(4-Hydroxyphenyl)hexyl clavulanate. Yield = 2.8%, colourless solid, m.p. 62-63°C.

Found: C, 63.8; H, 6.5; N, 3.8%

$C_{20}H_{25}NO_6$ requires: C, 64.0; H, 6.7; N, 3.7%

Example 35: R^2= $O(CH_2)_6$-(4-OCH_3)Ph, R^1 = OH

6-(4-Methoxyphenyl)hexyl clavulanate. Yield = 17%, yellow oil

Found: C, 64.6; H, 7.1; N, 3.6%

$C_{21}H_{27}NO_6$ requires: C, 64.8; H, 7.0; N, 3.6%

Examle 36: R^2= $O(CH_2)_6S$-(4-OH)Ph, R^1 = OH

6-(4-Hydroxyphenyl)thiohexyl clavulanate

(a) 6-Bromohexyl clavulanate

A mixture of 1,6-dibromohexane (15.37 g, 63mmol) and potassium clavulanate (3 g, 12.6mmol) in DMF (100ml) was stirred at room temperature for 20 hours. The mixture was evaporated in vacuo and partioned between ethyl acetate (50ml) and water

(50ml). The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated to an oil, which was purified by column chromatography on silica gel using 1:1 pet ether/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (3.8 g, 83%).

(b) 6-(4-Hydroxyphenyl)thiohexyl clavulanate.

A mixture of 6-bromohexyl clavulanate (1 g, 2.8mmol), 4-hydroxythiophenol (0.35g, 2.8mmol) and potassium carbonate (0.4 g, 2.8mmol) was stirred in acetone (50ml) for 20 hours, filtered and evaporated to a brown oil. The oil was purified by column chromatography on silia gel using 1:1 pet ether/ethyl acetate as the eluting solvents, yielding the product as a colourless oil (0.136 g, 12%).

Found: C, 58.5; H, 6.4; N, 3.2%

$C_{20}H_{25}NO_6S(0.09H_2O)$ requires: C, 58.9; H, 6.2; N, 3.4%

Example 37: R^2= $O(CH_2)_5S$-(4-OH,3,5-di-tert-butyl)Ph, R^1 = OH

5-(4-Hydroxy-3,5-di-tert-butylphenylthio)pentyl clavulanate

(a) 5-Bromopentyl clavulanate

A mixture of 1,5-dibromopentane (28.73 g, 0.125 mol) and potassium clavulanate (6 g, 0.025 mol) in DMF (200ml) was stirred at room temperature for 20 hours. The mixture was evaporated in vacuo and partitioned between ethyl acetate (100ml) and water (100ml). The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated to an oil, which was purified by column chromatography on silica gel using 1:1 pet ether/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (5.92 g, 68%).

(b) 5-(4-Hydroxy-3,5-di-tert-butylphenylthio)pentyl clavulanate

A mixture of 5-bromopentyl clavulanate (0.69 g, 2mmol), 4-hydroxy-3,5-di-tert-butylthiophenol (0.95g, 4mmol) and potassium carbonate (0.27 g, 2mmol) was stirred in acetone (50ml) for 20 hours, filtered and evaporated to an oil. The oil was purified by column chromatography on silica gel using 1:1 pet ether/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (0.70 g, 69%).

Found: C, 63.8; H, 7.9; N, 2.4;, S, 6.0%

$C_{27}H_{39}NO_6S$ requires: C, 64.1; H, 7.8; N, 2.8; S, 6.3%

Example 38: R^2= $O(CH_2)_5SPh$, R^1 = OH

5-Phenylthiopentyl clavulanate

A mixture of 5-bromopentyl clavulanate (Example 37a)(1.0 g, 2.8 mmol), thiophenol (0.35 g, 3.2mmol) and potassium carbonate (0.4 g, 2.8mmol) was stirred in acetone (50ml) for 20 hours, filtered and evaporated to a brown oil. The oil was purified

by column chromatography on silica gel using pet ether/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (0.44 g, 40%).
Found: C, 60.3; H, 6.2; N, 3.8%
$C_{19}H_{23}NO_5S$ requires: C, 60.5; H,6.1; N, 3.7%

Example 39: R^2= $OCH(C_5H_{11})Ph$, R^1 = OH
(RS)-2-Phenylhexyl (3R,5R)-clavulanate.

Examples 40-49 were prepared following the general procedures in J. Chem. Soc. Perkin Trans 1 1984, pp 635-650.

Example 40: R^2= $NH(CH_2)_6Ph$, R^1 = OH
N-6-Phenylhexyl clavulanamide
(a) Phenylhexyl iodide

Phenylhexyl bromide (82g, 0.34mol) and sodium iodide (157 g, 1.05mol) were stirred together in acetone (800ml) for 20 hours. The reaction mixture was evaporated to dryness and the residue was extracted with hexane, filtered and the filtrate was evaporated to dryness to yield the product as a pale yellow oil (97.9 g, 99%).

(b) Phenylhexyl phthalimide

Phenylhexyl iodide (25 g, 0.087mol) was dissolved in dry DMF (125ml) and potassium phthalimide (32.9 g, 0.178mol) was added and the mixture stirred at 100°C for 20 hours. Mixture was evaporated and the residue was treated with water (150ml) and washed with ethyl acetate (150ml, 100ml). The organic extracts were combined, washed with brine, dried ($MgSO_4$) and evaporated to a yellow solid which was purified by column chromatography on silica gel using 3:1 pet ether/ethyl acetate as the eluting solvents, yielding the product as a colourless oil which solidifies on standing (23.7 g, 88.7%)
m.p. 56-57°C.

(c) Phenylhexylamine

Phenylhexyl phthalimide (27.11g, 0.088mol) was dissolved in ethanol (750ml) and hydrazine monohydrate (12.9ml, 0.256mol) was added and the mixture was stirred at reflux for 19 hours. The reaction was filtered, evaporated to dryness and azeotroped with water (x2) and ethanol. Residue was mixed with diethyl ether, the solid was removed by filtration and the filtrate was evaporated to a yellow oil (10.3g). The solid was stirred with 2NNaOH (200ml) and ethyl acetate (200ml) and the mixture was filtered and the organic layer washed with brine, dried ($MgSO_4$) and evaporated to a yellow oil (6.2 g).

The two oils were combined and distilled in three batches using a Kugelrohr apparatus at 155°C/0.15mbar to give the product as a colourless oil (13.45 g , 86%).

(d) N-6-Phenylhexyl clavulanamide

A solution of benzyl clavulanate (4.26 g, 0.0147mol) in dry tetrahydrofuran (THF) (50ml) was hydogenated over 10% palladium on carbon (1.1 g) for 5 minutes at 25°C at 20psi. The catalyst was filtered off and the filtrate and solutions of dicyclohexylcarbodiimide (DCC) (2.53 g, 0.01226mol) in dry CH_2Cl_2 (175ml) and 6-phenylhexylamine (2.07 g, 0.0117mol) in dry CH_2Cl_2 (175ml) were mixed together quickly. The mixture was evaporated to near dryness and CH_2Cl_2 (175ml) was added. After stirring for 1 hour at room temperature the suspension was cooled, filtered and the filtrate evaporated to dryness. The residue was purified by column chromatography on silica gel using 2:1 ethyl acetate/hexane as the eluting solvents, yielding the crude product as a colourless solid (3.33 g, 80%). 1.03 g was further purified by chromatography and recrystallisation from diethyl ether to give an analytical sample as a colourless solid (0.24 g) m.p. 97-98° C.

Found: C, 67.0; H, 7.1; N, 8.0%

$C_{20}H_{26}N_2O_4$ requires: C, 67.0; H,7.3; N, 7.8%

Example 41: R^2= $NH(CH_2)_6$-(4-F)Ph, R^1 = OH

N-6-(4-Fluorophenyl)hexyl clavulanamide, Yield = 14.8% , cream solid, m.p. 106°C.

Found: C, 63.8; H, 6.6; N, 7.5%

$C_{20}H_{25}FN_2O_4$ requires: C, 63.8; H, 6.7; N, 7.4%

Example 42: R^2= $N(CH_3)(CH_2)_6$-(4-F)Ph, R^1 = OH

N-Methyl-6-(4-fluorophenyl)hexyl clavulanamide

(a) N-Methyl-N-6-(4-fluorophenyl)hexylamine

6-(4-Fluorophenyl)hexyl bromide (5 g, 0.0193mol) was stirred at reflux in 33% methylamine in ethanol (100ml) for 1.5h. The mixture was evaporated to dryness and the residue was stirred with ether and the white solid was collected by filtration (5.14 g), dissolved in 1N NaOH (100ml) and extracted with diethyl ether (2x75ml). The organic extracts were combined, washed with brine (75ml), dried ($MgSO_4$) and evaporated to give the product as a light brown oil (3.98 g, 99%).

(b) N-Methyl-6-(4-fluorophenyl)hexyl clavulanamide

Clavulanic acid (derived from benzyl calvulanate (5.18 g, 0.0179mol)as described in Example 40d) and N-methyl N-6-(4-fluorophenyl)hexylamine (3g, 0.0143mol) were reacted with DCC (3.07 g, 0.0149 mol) as described in Example 40d. Repeated column chromatography on silica gel using 2:1 ethyl acetate/hexane-ethyl acetate as the eluting

solvents yielded the product as a pale yellow oil (3.62g, 52%). A small sample was further purified for analysis.

Found: C, 64.3; H, 7.1; N, 6.7%

$C_{21}H_{27}FN_2O_4(0.045EtOAc, 0.053Et_2O)$ requires: C, 64.5; H, 7.1; N, 7.0%

Example 43: R^2= $N(CH_3)(CH_2)_6$- (4-C_4H_9)Ph, R^1 = OH

N-Methyl-6-(4-n-butylphenyl)hexyl clavulanamide. Yield = 15%, colourless oil.

Found: C, 69.7; H, 8.3; N, 6.4%

$C_{25}H_{36}N_2O_4$ requires: C, 70.1; H, 8.5; N, 6.5%

Example 44: R^2= $N(CH_3)CH_2Ph$, R^1 = OH

N-Methyl benzyl clavulanamide. Yield = 12%, foam.

Found: C, 63.8; H, 6.1; N, 9.4%

$C_{16}H_{18}N_2O_4$ requires: C, 63.6; H, 6.0; N, 9.3%

Example 45: R^2= $NH(CH_2)_4Ph$, R^1 = OH

N-4-Phenylbutyl clavulanamide. Yield = 17%, colourless solid, m.p. 74-76°C.

Found: C, 65.4; H, 6.6; N, 8.4%

$C_{18}H_{22}N_2O_4$ requires: C, 65.4; H, 6.7; N, 8.5%

Example 46: R^2= $NHCH_2Ph$, R^1 = OH

N-Benzyl clavulanamide. Yield = 14%, colourless solid, m.p. 140-142°C.

Found: C, 62.2; H, 5.6; N, 9.8%

$C_{15}H_{16}N_2O_4$ requires: C, 62.5; H, 5.6; N, 9.7%

Example 47: R^2= $NHO(CH_2)_6$-(4-C_4H_9)Ph, R^1 = OH

N-6-(4-n-Butylphenyl)hexyloxy clavulanamide

(a) 6-(4-n-Butylphenyl)hexyloxy phthalimide

6-(4-n-Butylphenyl)hexyl bromide (2 g, 0.00673mol) and N-hydroxyphthalimide (1.1 g, 0.00674mol) and triethylamine (1.4ml, 0.01mol) were mixed together in DMF (25ml) and stirred at 100°C for 6.5 hours. The mixture was evaporated to dryness and partitioned between water (50ml), brine (50ml) and ethyl acetate (75ml). The organic layer was separated and washed with 10% Na_2CO_3, brine (x2), dried ($MgSO_4$) and evaporated to a brown oil which was purified by column chromatography on silica gel using 1:1 CH_2Cl_2/hexane as the eluting solvents, yielding the product as a colourless solid (1.89 g, 74%) m.p. 36-39°C.

(b) 6-(4-n-Butylphenyl)hexyloxyamine

6-(4-n-Butylphenyl)hexyloxy phthalimide (1.83 g, 0.00482mol) was dissolved in glacial acetic acid (5ml) and 60%HBr (7ml) was added. The mixture was stirred at reflux for 10 minutes, cooled and diluted with 1N NaOH (100ml) and extracted with ethyl acetate (2x75ml). The organic extracts were combined, washed with brine, dried

($MgSO_4$) and evaporated to a brown oil which was purified by column chromatography on silica gel using 15:1 CH_2Cl_2/methanol as the eluting solvents yielding the product as an oil (0.94 g, 78%)

(c) N-6-(4-n-Butylphenyl)hexyloxy clavulanamide

A solution of benzyl clavulanate (1.2 g, 0.00415mol) in dry THF (35ml) was hydrogenated over 10% palladium on carbon (0.36 g) for 20 minutes at 25°C at 40psi. The catalyst was filtered off and the filtrate and solutions of DCC (0.84 g, 0.00407mol) in dry CH_2Cl_2 (100ml) and 6-(4-n-butylphenyl)hexyloxyamine (0.9 g, 0.00361mol) in dry CH_2Cl_2 (100ml) were mixed quickly together. The mixture was evaporated to near dryness and CH_2Cl_2 (100ml) was added. After stirring for 90 minutes at room temperature the suspension was filtered and the filtrate evaporated to dryness. Purification by repeat column chromatography on silica gel eluting with ethyl acetate/hexane and recrystallisation from ethyl acetate/hexane yielded the product as a white solid (0.29 g, 18.7%) m.p. 91-92°C.

Found: C, 66.8; H, 7.7; N, 6.5%

$C_{24}H_{34}N_2O_5$ requires: C, 67.0; H, 8.0; N, 6.5%

Example 48: R^2= $NHOCH_2Ph$, R^1 = OH

N-Benzyloxy clavulanamide. Yield = 13.3%, colurless solid, m.p.133-134°C.

Found: C, 59.1; H, 5.3; N, 9.2%

$C_{15}H_{16}N_2O_5$ requires: C, 59.2; H, 5.3; N, 9.2%

Example 49: R^2= $NHO(CH_2)_5Ph$, R^1 = OH

N-5-Phenylpentyloxy clavulanamide. Yield(crude) = 62%, colourless solid.

A sample was further purified for analysis. Colourless solid, m.p. 78-80°C.

Found: C 63.3; H, 6.6; N,7.8%

$C_{19}H_{24}N_2O_5$ requires: C, 63.3; H, 6.7; N, 7.8%

Example 50: R^2= NH-(4-CH_3)Ph, R^1 = OH

N-4-Tolyl clavulanamide

Solutions of potassium clavulanate (3 g, 0.0126mol) in water (19ml), p-toluidine hydrochloride (1.5 g, 0.0104mol) in water (19ml) and 1-cyclohexyl-3-(2-morpholinoethyl)-N-methylcarbodi-imidinium toluene-p-sulphonate (3.93 g 0.00928mol) in dioxane-water (19ml:38ml) were mixed at 0°C with stirring. After stirring for 80 minutes at 0-2°C, the precipitated toluamide was collected by filtration. The solid was recrystallised from ethyl acetate yielding the product as a white solid (0.47 g, 15.7%) m.p. 198-200°C.

Found: C, 62.4; H, 5.6; N, 9.9%

$C_{15}H_{16}N_2O_4$ requires: C, 62.5; H, 5.6; N, 9.7%

Example 51: R^2= $NHCH_2COPh$, R^1 = OH

N-Benzoylmethyl clavulanamide

Benzyl clavulanate (4.8 g, 0.0166mol) in dry THF (75ml) was hydrogenated over 10% palladium on carbon (1.2 g) for 15 minutes at 25°C at 40psi. The catalyst was removed by filtration and washed with THF (75ml) and the filtrate was cooled to -50°C under nitrogen and treated with pyridine (1.45ml, 0.0179mol) and isobutyl chloroformate (2.4ml, 0.0185mol). The reaction was stirred at -50 to -30°C for 40 minutes and then cooled to -40°C and N,N-diisopropylethylamine (3.1ml, 0.0178mol) was added. α-Aminoacetophenone hydrochloride (5.7 g, 0.0332mol) was added as a solid over 35 minutes and the reaction was stirred at -30°C for 90 minutes and poured into water (200ml) and extracted with ethyl acetate (200ml, 2x100ml). The organic extracts were combined, washed with 1N HCl, brine (x2), dried ($MgSO_4$) and evaporated to an orange solid which was dissolved in CH_2Cl_2 (50ml) and purified on a short silica gel column eluting with CH_2Cl_2 (50ml) and ethyl acetate (50ml). The filtrate was evaporated to dryness and the residue was mixed with hexane and the resulting cream solid was collected (1.19 g, 23%). 100mg was further purified by column chromatography on silica gel eluting with ethyl acetate and recrystallisation from ethyl acetate to give an analytical sample, colourless solid, m.p.164-165°C (32mg).

Found: C, 60.0; H, 5.1; N, 8.8%

$C_{16}H_{16}N_2O_5(0.18H_2O, 0.014EtOAc)$ requires: C, 60.1; H, 5.2; N, 8.7%

Example 52: R^2= OCH_3, R^1 = OH

Methyl (3R, 5R, E) clavulanate

Example 53: R^2= $O(CH_2)_6Ph$, R^1 = $OCOCH_3$

6-Phenylhexyl O-acetylclavulanate

6-Phenylhexyl clavulanate (0.94 g, 2.6mmol) was dissolved in dry dichloromethane (CH_2Cl_2) (20ml). The solution was cooled to -30°C and treated with pyridine (0.21 g, 27mmol) followed by the dropwise addition of acetyl chloride (0.21 g, 27mmol) in CH_2Cl_2 (20ml). Stirring was continued at -30°C for 60 minutes and the reaction mixture was poured into 1N HCl (25ml), extracted with CH_2Cl_2 (15ml) and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to a yellow oil, which was purified by column chromatography on silica gel using 2:1 pet ether/ethyl acetate as the eluting solvents, yielding the product as a colourless oil (0.40 g, 38%).

Found: C, 65.7; H, 6.7; N, 3.6%

$C_{22}H_{27}NO_6$ requires: C, 65.8; H, 6.8; N, 3.5%

The following compounds, Examples 54-95, were prepared as above using the appropriate acid chloride.

Example 54: R^2= OCH_2-(4-NO_2)Ph, R^1 = OCO-(4-Ph)Ph
4-Nitrobenzyl O-(4-biphenylcarbonyl)clavulanate. Yield = 52%, pale yellow solid
m.p. 119-120°C
Found: C, 65.1; H, 4.5; N, 5.6%
$C_{28}H_{22}N_2O_8$ requires: C, 65.4; H, 4.3; N, 5.4%
Example 55: R^2= $O(CH_2)_6$-(4-Br)Ph, R^1 = $OCOCH_3$
6-(4-Bromophenyl)hexyl O-acetylclavulanate. Yield = 83%, yellow oil.
Found: C, 54.7; H, 5.5; N, 3.2; Br, 16.9%
$C_{22}H_{26}BrNO_6$ requires: C, 55.0; H, 5.5; N, 2.9; Br, 16.6%
Example 56: R^2= $O(CH_2)_6$-(4-Br)Ph, R^1 = OCO-(4-Ph)Ph
6-(4-Bromophenyl)hexyl O-(4-biphenylcarbonyl)clavulanate. Yield = 32%,
colourless solid, m.p. 94-95°C.
Found: C, 63.9; H, 5.3; N, 2.5; Br, 13.1%
$C_{33}H_{32}BrNO_6$ requires: C, 64.1, H, 5.2; N, 2.3; Br, 12.9%
Example 57: R^2= $O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = $OCOCH_3$
6-(4-n-Butylphenyl)hexyl O-acetylclavulanate, Yield = 76%, pale yellow oil.
Found: C, 68.1; H, 7.5; N, 3.1%
$C_{26}H_{35}NO_6$ requires: C, 68.3; H, 7.7; N, 3.1%
Example 58: R^2= $O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = OCOPh
6-(4-Butylphenyl)hexyl O-benzoylclavulanate, Yield = 67%, yellow oil.
Found: C, 71.6; H, 7.2; N, 2.8%
$C_{31}H_{37}NO_6$ requires: C, 71.7; H, 7.2; N, 2.7%
Example 59: R^2= $O(CH_2)_6$-(4-Cl)Ph, R^1 = $OCOCH_3$
6-(4-Chlorophenyl)hexyl O-acetylclavulanate, Yield = 50%, yellow oil.
Found: C, 59.7; H, 6.0; N, 3.3; Cl, 8.8%
$C_{22}H_{26}ClNO_6(0.06CH_2Cl_2)$ requires: C, 60.1; H, 6.0; N, 3.2; Cl, 9.0%
Example 60: R^2= OCH_2-(2,4-diCl)Ph, R^1 = OCOPh
2,4-Dichlorobenzyl O-benzoylclavulanate, Yield = 18%, colourless solid, m.p. 79°C.
Found: C, 57.1; H, 3.8; N, 3.0; Cl, 15.5%
$C_{22}H_{17}Cl_2NO_6$ requires: C, 57.2; H, 3.7; N, 3.0; Cl, 15.3%
Example 61: R^2= OCH_2-(2.4-diCl)Ph, R^1= $OCOCH_3$
2.4-Dichlorobenzyl O-acetylclavulanate, Yield = 45%, colourless solid, m.p. 57-58°C
Found: C, 51.0; H, 3.9; N, 3.6; Cl, 17.6%

$C_{17}H_{15}Cl_2NO_6$ requires: C, 51.0; H, 3.8; N, 3.5; Cl, 17.7%

Example 62: R^2= OCH_2Ph, R^1 = $OCOCH_3$

O-Acetyl benzyl clavulanate, Yield = 75%, yellow oil.

Found: C, 61.9; H, 5.3; N, 4.8%

$C_{17}H_{17}NO_6$ requires: C, 61.6; H, 5.2; N, 4.2%

Example 63: R^2= OCH_2Ph, R^1 = OCO-(4-Ph)Ph

Benzyl O-(4-biphenylcarbonyl)clavulanate, Yield = 33%, glass.

Found: C, 71.3; H, 5.1; N, 3.1%

$C_{28}H_{23}NO_6(0.032CH_2Cl_2)$requires: C, 71.3; H, 4.9; N, 3.0%

Example 64: R= OCH_2Ph, R^1 = OCOPh

O-Benzoyl benzyl clavulanate, Yield = 47%, pale yellow oil.

Found: C, 66.5; H, 5.1; N, 3.5%

$C_{22}H_{19}NO_6$ requires: C, 66.2; H, 4.9; N, 3.6%

Example 65: R^2= OCH_2Ph, R^1 = $OCO(CH_2)_2Ph$

Benzyl O-phenpropionylclavulanate, Yield = 56%, pale yellow oil.

Found: C, 68.7; H, 5.6; N, 3.4%

$C_{24}H_{23}NO_6$ requires: C, 68.4; H, 5.5; N, 3.3%

Example 66: R^2= OCH_2Ph, R^1 = $OCOCH_2Ph$

Benzyl O-phenylacetylclavulanate, Yield = 38%, pale yellow oil.

Found: C, 67.7; H, 5.3; N, 3.3%

$C_{23}H_{21}NO_6$ requires: C, 67.8; H, 5.2; N, 3.4%

Example 67: R^2= OCH_2Ph, R^1 = $OCO(CH_2)_4CH_3$

Benzyl O-hexanoylclavulanate, Yield = 72%, yellow oil.

Found: C, 64.8; H, 6.5; N, 3.6%

$C_{21}H_{25}NO_6$ requires: C, 65.0; H, 6.5; N, 3.6%

Example 68: R^2= OCH_2Ph, R^1 = $OCO(CH_2)_8CH{=}CH_2$

Benzyl O-(10-undecanoyl)clavulanate, Yield = 71%, pale yellow oil.

Found: C, 68.8; H, 7.5; N, 3.1%

$C_{26}H_{33}NO_6$ requires: C, 68.6; H, 7.3; N, 3.1%

Example 69: R^2= OCH_2Ph, R^1 = OCO-(1-adamantyl)

Benzyl O-(1-adamantylcarbonyl)clavulanate, Yield = 44%, pale yellow oil.

Found: C, 67.1; H, 6.6; N, 3.0%

$C_{26}H_{29}NO_6(0.2CH_2Cl_2)$ requires: C, 67.2; H, 6.3; N, 3.0%

Example 70: R^2= OCH_2Ph, R^1 = $OCOCH_2$-(2-thienyl)

Benzyl O-(2-thienylacetyl)clavulanate, Yield = 74%, pale yellow oil.

Found: C, 60.5; H, 4.7; N, 3.2%

$C_{21}H_{19}NO_6S(0.1CH_2Cl_2)$ requires: C, 60.3; H, 4.6; N, 3.3%

Example 71: R^2= OCH_2Ph, R^1 = $OCO(CH_2)_2CO_2Et$

Benzyl O-(ethylsuccinoyl)clavulanate. Yield = 52%, pale yellow oil.

Found: C, 60.5; H, 5.6; N, 3.1%

$C_{21}H_{23}NO_8$ requires: C, 60.4; H, 5.6; N, 3.4%

Example 72: R= OCH_2Ph, R^1 = OCO-(4-CN)Ph

Benzyl O-(4-cyanobenzoyl)clavulanate. Yield = 52%, thick yellow oil.

Found: C, 64.9; H, 4.4; N, 6.4%

$C_{23}H_{18}N_2O_6(0.1CH_2Cl_2)$ requires: C, 65.0; H, 4.3; N, 6.6%

Example 73: R^2= OCH_2Ph, R^1 = OCO-(4-NO_2)Ph

Benzyl O-(4-nitrobenzoyl)clavulanate. Yield = 49%, pale yellow oil.

Found: C, 59.5; H, 4.3; N, 6.0%

$C_{22}H_{18}N_2O_8(0.1CH_2Cl_2)$ requires: C, 59.4; H, 4.1; N, 6.3%

Example 74: R^2= OCH_2Ph, R^1 = $OCOCH(Ph)_2$

Benzyl O-(diphenylacetyl)clavulanate. Yield = 53%, pale yellow glass.

Found: C, 70.9; H, 5.3; N, 2.8%

$C_{29}H_{25}NO_6(0.1CH_2Cl_2)$ requires: C, 71.0; H, 5.2; N, 2.9%

Example 75: R^2= OCH_2Ph, R^1 = $OCO(CH_2)_7CH_3$

Benzyl O-nonoylclavulanate. Yield = 81%, pale yellow oil.

Found: C, 66.9; H, 7.1; N, 3.2%

$C_{24}H_{31}NO_6$ requires: C, 67.1; H, 7.3; N, 3.3%

Example 76: R^2= OCH_2Ph, R^1 = $OCO(CH_2)_2$-C_5H_9

Benzyl O-(3-cyclopentylpropionyl)clavulanate. Yield = 34%, pale yellow oil.

Found: C, 66.5; H, 6.6; N, 3.6%

$C_{23}H_{27}NO_6$ requires: C, 66.8; H, 6.6; N, 3.4%

Example 77: R^2= OCH_2Ph, R^1 = OCO-$(CH_2)_5Ph$

Benzyl O-(6-phenylhexyl)clavulanate. Yield = 33%, pale yellow oil.

Found: C, 70.0; H, 6.4; N, 3.3%

$C_{27}H_{29}NO_6$ requires: C, 70.0; N, 6.3; N, 3.0%

Example 78: R^2= OCH_2Ph, R^1 = OCO-(1-naphthyl)

Benzyl O-(1-naphthoyl)clavulanate. Yield = 39%, pale yellow oil.

Found: C, 69.3; H, 4.9; N, 3.2%

$C_{26}H_{21}NO_6(0.4H_2O)$ requires: C, 69.4; H, 4.9; N, 3.1%

Example 79: R^2= OCH_2Ph, R^1 = $OCOC_6H_{11}$

Benzyl O-(cyclohexylcarbonyl)clavulanate. Yield = 46%, pale yellow oil.

Found: C, 66.3; H, 6.4; N, 3.2%

$C_{22}H_{25}NO_6$ requires: C, 66.2; H, 6.3; N, 3.5%

Example 80: R^2= OCH_2Ph, R^1 = $OCO(4\text{-}CH_2Ph)Ph$

Benzyl O-(4-benzylbenzoyl)clavulanate. Yield = 40%, pale yellow oil.

Found: C, 70.2; H, 5.3; N, 2.6%

$C_{29}H_{25}NO_6(0.15CH_2Cl_2)$ requires: C, 70.6; H, 5.1; N, 2.8%

Example 81: R^2= OCH_2Ph, R^1 = $OCO(4\text{-}O\text{-}Ph)Ph$

Benzyl O-(phenoxybenzoyl)clavulanate. Yield = 24%, cream solid, m.p. 83-85°C.

Found: C, 68.2; H, 4.8; N, 2.9%

$C_{28}H_{23}NO_7(0.125CH_2Cl_2)$ requires: C, 68.1; H, 4.7; N, 2.8%

Example 82: R^2= $NH(CH_2)_6Ph$, R^1 = $OCOCH_3$

N-6-Phenylhexyl O-acetylclavulanamide, Yield = 77%, colourless solid,

m.p. 62-63°C

Found: C, 65.7; H, 6.9; N, 7.0%

$C_{22}H_{28}N_2O_5$ requires: C, 66.0; H, 7.1; N, 7.0%

Example 83: R^2= $(CH_2)_6\text{-}(4\text{-}OCH_3)Ph$, R^1 = $OCOCH_3$

6-(4-Methoxyphenyl)hexyl O-acetylclavulanate. Yield = 23%, colourless oil.

Found: C, 64.0; H, 6.9; N, 3.4%

$C_{23}H_{29}NO_7$ requires: C, 64.0; H, 6.8; N, 3.3%

Example 84: R^2= $NHO(CH_2)_5Ph$, R^1 = $OCOCH_3$

N-5-Phenylpentyloxy O-acetylclavulanamide, Yield = 54%, yellow oil.

Found: C, 62.4; H, 6.6; N, 7.1%

$C_{21}H_{26}N_2O_6$ requires: C, 62.7; H, 6.5; N, 7.0%

Example 85: R^2= $NH(CH_2)_6\text{-}(4\text{-}F)Ph$, R^1 = $OCOCH_3$

N-6-(4-Flurophenyl)hexyl O-acetylclavulanamide. Yield = 30%, colourless solid,

m.p. 64-65°C.

Found: C, 63.0; H, 6.4; N, 6.9%

$C_{22}H_{27}FN_2O_5$ requires: C, 63.1; H, 6.5; N, 6.7%

Example 86: R^2= $N(CH_3)(CH_2)_6\text{-}(4\text{-}F)Ph$, R^1 = $OCOCH_3$

N-Methyl-6-(4-fluorophenyl)hexyl O-acetylclavulanamide, Yield = 73%, colourless oil.

Found: C, 63.6; H, 7.1; N, 6.3%

$C_{23}H_{29}FN_2O_5$ requires: C, 63.9; H, 6.8; N, 6.5%

Example 87: R^2= $O(CH_2)_5CO\text{-}(4\text{-}Cl)Ph$, R^1 = $OCOCH_3$

O-Acetyl 6-(4-chlorophenyl)-6-oxo-hexyl clavulanate. Yield = 64%, yellow oil.

Found: C, 57.6; H, 5.4; N, 3.0; Cl, 8.7%

$C_{22}H_{24}ClNO_7(0.75CH_2Cl_2)$ requires: C, 58.1; H, 5.3; N, 3.1; Cl, 8.9%

Example 88: R^2= $O(CH_2)_6\text{-}(4\text{-}F)Ph$, R^1 = $OCOCH_3$

6-(4-Fluorophenyl)hexyl O-acetylclavulanate. Yield = 46%. colourless oil.
Found: C, 62.9; H, 6.3; N, 3.1%
$C_{22}H_{26}FNO_6$ requires: C, 63.0; H, 6.3; N, 3.3%
Example 89: R^2= $O(CH_2)_6$-(4-Cl)Ph, R^1 = $OCOCHCl_2$
6-(4-Chlorophenyl)hexyl O-dichloroacetylclavulanate. Yield = 79%, yellow oil.
Found: C, 52.6; H, 4.9; N, 2.7%
$C_{22}H_{24}Cl_3NO_6$ requires: C, 52.4; H, 4.8; N, 2.8%
Example 90: R^2= OCH_2-(3,4-diCl)Ph, R^1 = OCOPh
3,4-Dichlorobenzyl O-benzoylclavulanate, Yield = 50%, yellow oil.
Found: C, 57.1; H, 3.9; N, 2.9; Cl, 15.2%
$C_{22}H_{17}Cl_2NO_6$ requires: C, 57.2; H, 3.7; N, 3.0; Cl, 15.3%
Example 91: R^2= OCH_2-(3,4-diCl)Ph, R^1 = $OCOCH_3$
3,4-Dichlorobenzyl O-acetylclavulanate. Yield = 74%. pale yellow oil.
Found: C, 51.1; H, 3.9; N, 3.5; Cl, 17.2%
$C_{17}H_{15}Cl_2NO_6(0.06Et_2O)$ requires: C, 51.2; H, 3.9; N, 3.5; Cl, 17.5%
Example 92: R^2= $N(CH_3)(CH_2)_6$-(4-C_4H_9)Ph, R^1 = OCOPh
N-Methyl-6-(4-n-butylphenyl)hexyl O-benzoylclavulanamide. Yield = 50%, colourless oil.
Found: C, 72.1; H, 7.5; N, 5.1%
$C_{32}H_{40}N_2O_5$ requires: C, 72.1; H, 7.6; N, 5.3%
Example 93: R^2= $NHO(CH_2)_6$-(4-C_4H_9)Ph, R^1 = $OCOCH_3$
N-6-(4-n-Butylphenyl)hexyloxy O-acetylclavulanamide. Yield = 43%, colourless solid, m.p. 67-68°C.
Found: C, 65.7; H, 7.4; N, 6.1%
$C_{26}H_{36}N_2O_6$ requires: C, 66.1; H, 7.7; N, 5.9%
Example 94: R^2= $N(CH_3)(CH_2)_6$-(4-C_4H_9)Ph, R^1 = $OCOCH_3$
N-Methyl-6-(4-n-butylphenyl)hexyl O-acetylclavulanamide. Yield = 44%, colourless oil.
Found: C, 69.1; H, 8.1; N, 5.9%
$C_{27}H_{38}N_2O_5$ requires: C, 68.9; H, 8.1; N, 6.0%
Example 95: R^2= OCH_2Ph, R^1 = $OCOCHCl_2$
Benzyl O-dichloroacetylclavulanate. Yield = 82%(crude)
Analytical sample, yellow oil.
Found: C, 51.6; H, 4.0; N, 3.5%
$C_{17}H_{15}Cl_2NO_6(0.13C_6H_{14})$ requires: C, 51.9; H,4.1; N, 3.4%
Example 96: R^2= $N(OH)(CH_2)_6$-(4-F)Ph, R^1 = $OCOCH_3$
N-Hydroxy-N-6-(4-fluorophenyl)hexyl O-acetylclavulanamide
(a) Benzyl O-acetylclavulanate

Benzyl clavulanate (4 g, 0.0138mol) was dissolved in dry CH_2Cl_2 (75ml). The solution was cooled to -30°C under nitrogen and treated with pyridine (1.3ml, 0.01607mol) and acetyl chloride (1ml, 0.0141mol). The reaction was stirred at -30°C to -10°C over 2 hours and poured into 0.5N HCl (100ml) and CH_2Cl_2 (50ml). The organic layer was removed, washed with brine, dried ($MgSO_4$) and evaporated to a yellow oil which was purified by column chromatography on silica gel using 2:1 hexane/ethyl acetate as the eluting solvents, yielding the product as an oil (4.14 g, 90%).

(b) Ethyl 2-(6-(4-fluorophenyl)hexyl)-3-methyl-isoxazol-5-one-4-carboxylate

A solution of ethyl 5-hydroxy-3-methyl-4-isoxazolecaroxylate, sodium salt, hemihydrate (4.9 g, 0.0242mol) in dry DMF (20ml) was treated with 6-(4-fluorophenyl)hexyl bromide (7.4 g, 0.0242mol) and stirred at 120°C for 1 hour, poured into water (300ml) and extracted with CH_2Cl_2 (3x75ml). The organic extracts were combined, washed with water, dried ($MgSO_4$) and evaporated to an orange oil which was purified by column chromatography on silica gel using 1:1 ethyl acetate/hexane as the eluting solvents, yielding the product as a cream solid (6.11 g, 72%) m.p. 69-71°C.

(c) N-6-(4-fluorophenyl)hexyl hydroxylamine

Ethyl 2-(6-(4-fluorophenyl)hexyl)-3-methyl-isoxazol-5-one-4-carboxylate (5.8 g, 0.0166mol) was dissolved in water (15ml), glacial acetic acid (15ml) and cHCl (15ml), stirred at reflux for 19 hours and evaporated to dryness. The residue was dissolved in water (50ml) and basified with 2N NaOH to pH14 and extracted with ethyl acetate (2x75ml), dried ($MgSO_4$) and evaporated to an orange oil, triturated with hexane and the solid product was collected by filtration, yielding the product as a cream solid (2.28 g, 65%) m.p. 74-75°C.

(d) N-Hydroxy-N-6-(4-fluorophenyl)hexyl O-acetylclavulanamide

Benzyl O-acetyl clavulanate (2.45 g, 0.00739mol) was hydrogenated in dry THF (50ml) over 10% palladium on carbon (1 g) for 7 minutes at 25°C at 20psi. The reaction mixture was filtered to remove catalyst and THF (50ml) was added. The filtrate and solutions of DCC (1.27 g, 0.00616mol) in dry CH_2Cl_2 (100ml) and N-6-(4-fluorophenyl)hexyl hydroxylamine (1.25 g, 0.00592mol) in dry CH_2Cl_2 (100ml) were mixed together quickly. The mixture was evaporated to near dryness and CH_2Cl_2 (100ml) was added. After stirring for 90 minutes at room temperature the mixture was filtered and evaporated to an oil which was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (0.183 g, 7.1%)

Found: C, 60.8; H, 6.4; N, 6.3%

$C_{22}H_{27}FN_2O_6$ requires: C, 60.8; H, 6.3; N, 6.5%

Example 97: R^2= $N(OCOCH_3)(CH_2)_6$-(4-F)Ph. R^1 = $OCOCH_3$
N-Acetoxy-N-6-(4-fluorophenyl)hexyl O-acetylclavulanamide

A solution of N-Hydroxy-N-6-(4-fluorophenyl)hexyl O-acetylclavulanamide (1 g, 0.0023mol) in dry CH_2Cl_2 (60ml), cooled to -30°C under nitrogen, was treated with pyridine (0.21ml, 0.0026mol) followed a solution of acetyl chloride (0.18 g, 0.002306mol) in CH_2Cl_2 (5ml). The reaction was stirred at -30°C to 0°C over 90 minutes, poured into brine (100ml) with CH_2Cl_2 (50ml). The organic layer was separated, dried ($MgSO_4$) and evaporated to a yellow oil which was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (0.49 g, 45%).

Found: C, 60.3; H, 6.2; N, 5.7%

$C_{24}H_{29}FN_2O_7$ requires: C, 60.5; H, 6.1; N, 5.9%

Example 98: R^2= $N(OCOCH_3)(CH_2)_6$-(4-C_4H_9)Ph. R^1 = $OCOCH_3$
N-Acetoxy-6-(4-n-butylphenyl)hexyl O-acetylclavulanamide

(a) N-Hydroxy-N-6-(4-n-butylphenyl)hexyl clavulanamide

Clavulanic acid (derived from benzyl clavulanate (0.6 g, 0.00207) as described in Example 40d) and N-6-(4-n-butylphenyl)hexyl hydroxylamine (prepared as described for Example 96b) were treated with DCC (0.42 g, 0.00203mol) as described in Example 96d Purification of the residue by column chromatography on silica gel using hexane/ethyl acetate as the eluting solvents, gave the product as an oil (0.15g, 29%)

(b) N-Acetoxy-6-(4-n-butylphenyl)hexyl O-acetylclavulanamide

N-Hydroxy-N-6-(4-n-butylphenyl)hexyl clavulanamide (0.14 g, 0.000325) was dissolved in dry CH_2Cl_2 (20ml). The solution was cooled to -30°C under nitrogen and treated with pyridine (0.03ml, 0.00037mol) and a solution of acetyl chloride (0.023ml, 0.000323mol) in CH_2Cl_2 (1ml), stirred at -30°C for 1 hour, poured into brine (50ml) and extracted with CH_2Cl_2 (30ml). The organic layer was dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography on silica gel using 3:1 hexane/ethyl acetate as the eluting solvents, yielding the product as a pale yellow oil (0.059 g, 70%)

Found: C, 64.9; H, 7.3; N, 5.1%

$C_{28}H_{38}N_2O_7$ requires: C, 65.3; H, 7.4; N, 5.4%

Example 99: R^2= $NHO(CH_2)_6Ph$. R^1 = $OCOCH_3$
N-6-Phenylhexyloxy O-acetylclavulanamide. Yield = 42%, colourless solid, m.p. 70-71°C.

A solution of benzyl O-acetylclavulanate (Example 96a) (1.4 g, 0.00422 mol) in dry THF (42ml) was hydrogenated over 10% palladium on carbon (0.56 g) for 5 minutes at 25°C at 20psi. The catalyst was filtered off and the filtrate and solutions of DCC (0.73 g, 0.00354mol) in dry CH_2Cl_2 (65ml) and 6-phenylhexyloxyamine (prepared as for

Example 47b) (0.65 g, 0.00336mol) in dry CH_2Cl_2 (65ml) were mixed together quickly. The reaction mixture was evaporated to near dryness and CH_2Cl_2 (65ml) was added. After stirring at room temperature for 1.5 hours the suspension was cooled, filtered and the filtrate was evaporated to dryness. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluting solvents and recrystallisation from ethyl acetate/hexane gave the product as a colourless solid (0.59 g, 42%) m.p. 70-71°C.

Found: C, 62.6; H, 6.5; N, 6.8%

$C_{22}H_{28}N_2O_6(0.23H_2O)$ requires: C, 62.8; H, 6.8; N, 6.7%

Example 100: $R^2 = O(CH_2)_6$-(4-F)Ph, R^1 = OCHO

6-(4-Fluorophenyl)hexyl O-formylclavulanate

98-100% Formic acid (0.12ml, 0.00318mol) was added to acetic anhydride (0.25ml, 0.00265mol) at 0°C. The mixture was then stirred at 50°C for 90 minutes, cooled to 0°C, (THF) (1ml) was added followed by 6-(4-fluorophenyl)hexyl clavulanate (0.5 g, 0.00132mol) in dry THF (1ml) and the reaction was stirred at room temperature for 4 hours. The reaction mixture was evaporated and purified by column chromatography on silica gel using 3:1 hexane/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (0.23 g, 43%).

Found: C, 62.2; H, 6.2; N, 3.4%

$C_{21}H_{24}FNO_6$ requires: C, 62.2; H, 6.0; N, 3.5%

Example 101: $R^2 = O(CH_2)_6Ph$, $R^1 = N(CH_3)CH_2Ph$

6-Phenylhexyl 9-N-benzyl-N-methyldeoxy clavulanate

6-Phenylhexyl O-dichloroacetylclavulanate (1g, 2mmol) was dissolved in DMF (20ml) at 0°C and treated with N-benzylmethylamine (0.46g, 3.8mmol) dropwise. The mixture was stirred for 3 hours then poured into ethyl acetate (40 ml), washed with water (x3), brine (x2), dried ($MgSO_4$) and evaporated to a yellow oil which was purified by repeat column chromatography on silica gel using 1:1 pet ether/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (0.037 g, 4%).

Found: C, 71.6; H, 7.4; N, 5.6%

$C_{28}H_{34}N_2O_4(0.04H_2O)$ requires: C, 71.6; H, 7.5; N, 6.0%

Example 102: $R^2 = O(CH_2)_6$-(4-F)Ph, R^1 = NHCHO

6-(4-Fluorophenyl)hexyl 2-(2-formamidoethylidene)-clavam-3-carboxylate

(a) N-Formyl benzyl carbamate

Benzyl carbamate (20g, 0.1323mol) and N,N-dimethylformamide dimethylacetal (52ml, 0.391mol) were heated together at 120°C for 15 minutes. The methanol was removed and the reaction mixture was heated at 100°C for 1 hour, cooled and filtered to

give a colourless solid (21.2 g) m.p. 80-82°C. which was mixed with 70% aqueous glacial acetic acid (100ml) and stirred at room temperature for 1 hour. poured into water (500ml) and extracted with ethyl acetate (2x250ml). The organic extracts were combined. washed with water. brine. dried ($MgSO_4$) and evaporated in vacuo. The residue was mixed with water. filtered and the solid was recrystallised from ethanol/water to give the product as colourless needles (12.97 g. 55%). m.p. 65°C.

(b) 6-(4-Fluorophenyl)hexyl-2-(2-formamidoethylidene)-clavam-3-carboxylate

A solution of 6-(4-flurophenyl)hexyl clavulanate (3 g. 0.00795mol) in dry THF (90ml). stirred at 10°C under nitrogen. was treated with triphenylphosphine (2.4 g, 0.00915mol) and N-formyl benzyl carbamate (2.85 g, 0.0159mol). Diethylazodicarboxylate (1.59 g, 0.00913mol) in dry THF (30ml) was added over 20 minutes and the reaction mixture was stirred at room temperature for 21 hours and evaporated to an orange oil which was purified by column chromatography on silica gel using 2:1 hexane/ethyl acetate as the eluting solvents to give a yellow oil (4.06 g). This oil was hydrogenated in dry THF (50ml) over 10% palladium on carbon (2 g) for 60 minutes at 25°C at 40psi. The reaction mixture was filtered to remove catalyst. evaporated to an oil which was purified by column chromatograhy on silica gel eluting with hexane/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (0.146 g, 4.5%).

Found: C. 61.9; H, 6.2; N. 6.8%

$C_{21}H_{25}FN_2O_5$ requires: C, 62.3; H, 6.2; N, 6.9%

Example 103: $R^2 = O(CH_2)_6Ph$, $R^1 = NHCHO$

6-Phenylhexyl-2-(2-formamidoethylidene)-clavam-3-carboxylate

Potassium cyanate (6.19 g. 0.0763mol) in water (5ml) and toluene (75ml) was cooled to -5° C. 5N H_2SO_4 (12.5ml) was added to the vigorously stirred solution over 5 minutes keeping the temperature below 0°C. The toluene layer was decanted off. dried ($MgSO_4$) and cooled to -10 °C and added to a solution of 6-phenylhexyl clavulanate (1 g, 0.00278mol) and triphenyl phosphine (0.93 g, 0.00354mol) in dry THF (20ml) stirred at -10°C. Diethylazodicarboxylate (0.62ml, 0.00394mol) was added at -10°C and the reaction mixture was stirred at room temperature for 1 hour. filtered and evaporated in vacuo. The residue was dissolved in dry CH_2Cl_2 (25ml) and cooled to 10°C. Pyridine (0.56ml. 0.00692mol) and formic acid (0.25ml. 0.00663mol) were added and the reaction was srirred at room temperature for 1 hour and diluted with CH_2Cl_2 (75ml). The reaction mixture was washed with 0.5N HCl. water. 10% $NaHCO_3$. brine. dried $MgSO_4$ and evaporated to a brown oil which was purified by column chromatography on silica gel eluting with ethyl acetate and

recrystallisation from diethyl ether to give the product as a colourless solid (0.037 g, 3.4%), m.p. 53-54°C.

Found: C, 65.1; H, 6.6; N, 7.4%

$C_{21}H_{26}N_2O_5$ requires: C, 65.3; H, 6.8; N, 7.3%

Examples 104 and 105: $R^2 = O(CH_2)_6Ph$, $R^1 = NHCOCH_3$

(i) 6-Phenylhexyl (3R, 5R, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate and

(ii) 6-Phenylhexyl (3R, 5R, E)-2-(2-acetamidoethylidene)-clavam-3-carboxylate

(a) N-Acetyl benzyl carbamate

To a suspension of benzyl carbamate (20 g, 0.1323mol) in dry benzene (20ml) was added acetyl chloride (21ml, 0.2953mol)and the mixture was stirred at 75°C for 20 hours. Acetyl chloride (5ml, 0.0703mol) was added and the reaction mixture was stirred at 75°C for 1 hour and then evaporated to dryness. The residue was azeotroped with ethyl acetate (x2) and the resulting yellow solid was recrystallised from ethyl acetate/hexane to give the product as a colourless solid (18.49 g, 72%), m.p.106-108°C

(b) (i) 6-Phenylhexyl (3R, 5R, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate and (ii) 6-Phenylhexyl (3R, 5R, E)-2-(2-acetamidoethylidene)-clavam-3-carboxylate

A solution of 6-phenylhexyl clavulanate (4.5 g, 0.0125mol) in dry THF (100ml), stirred at 10°C under nitrogen, was treated with triphenylphosphine (3.78 g, 0.0144mol) and N-acetyl benzyl carbamate (2.9 g, 0.015mol). Diethylazo dicarboxylate (2.51 g, 0.0144mol) in dry THF (30ml) was added over 10 minutes. The reaction mixture was then stirred at room temperature for 5 hours and evaporated to an oil which was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluting solvents, yielding a crude oil (0.96 g). This oil was hydrogenated in dry THF (30ml) over 10% palladium on carbon (0.5 g) for 60 minutes at 25°C at 40psi. The reaction was filtered to remove catalyst, evaporated to an oil which was purified by column chromatograhy on silica gel eluting with 2:1 ethyl acetate/hexane as eluting solvents. Recrystallisation from ether/hexane of the appropriate column fractions gave:

i) as a colourless solid (0.222g, 4.45%), m.p. 64-65°C.

Found: C, 65.6; H, 6.9; N, 7.0%

$C_{22}H_{28}N_2O_5$ requires: C, 66.0; H,7.1; N, 7.0%

(ii) as a colourless solid (0.02g, 0.4%) m.p. 64-65°C

Found: C, 65.8; H, 6.9; N, 7.1%

$C_{22}H_{28}N_2O_5$ requires: C, 66.0; H, 7.1; N, 7.0%

The following compounds, Examples 106-109, were prepared as described above in Example 104

Example 106: $R^2 = O(CH_2)_6$-(4-F)Ph, $R^1 = NHCOCH_3$
6-(4-Fluorophenyl)hexyl-2-(2-acetamidoethylidene)-clavam-3-carboxylate. Yield = 34%, colourless solid, m.p. 73-74°C.
Found: C, 63.2; H, 6.4; N, 6.7%
$C_{22}H_{27}FN_2O_5$ requires: C, 63.2; H, 6.5; N, 6.7%
Example 107: $R^2 = O(CH_2)_6$-(4-Cl)Ph, $R^1 = NHCOCH_3$
6-(4-Chlorophenyl)hexyl-2-(2-acetamidoethylidene)-clavam-3-carboxylate. Yield = 5%, colourless solid, m.p. 69-72°C.
Found: C, 61.2; H, 6.2; N, 6.5%
$C_{22}H_{27}ClN_2O_5$ requires: C, 60.8; H, 6.3; N, 6.4%
Example 108: $R^2 = O(CH_2)_6$-(4-C_4H_9)Ph, $R^1 = NHCOCH_3$
6-(4-n-Butylphenyl)hexyl (3R, 5R, Z)-2-(2-acetamidoethylidene)clavam-3-carboxylate, Yield = 20%, colourless solid, m.p. 80-82°C.
Found: C, 68.2; H, 7.8; N, 6.4%
$C_{26}H_{36}N_2O_5$ requires: C, 68.4; H, 8.0; N, 6.1%BRL-23845
Example 109: $R^2 = OCH_2Ph$, $R^1 = NHCOCH_3$
Benzyl (3R, 5R, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate. Yield = 3%, colourless solid, m.p. 134-135°C
Found: C, 61.8; H, 5.5; N, 8.4%
$C_{17}H_{18}N_2O_5$ requires: C, 61.8; H, 5.5; N, 8.5%
Example 110: $R^2 = OCH_2Ph$, $R^1 = NHCOPh$
(i) Benzyl (3R, 5R, Z)-2-(2-benzamidoethylidene)-clavam-3-carboxylate
and
Example 111 $R^2 = OCH_2Ph$, $R^1 = NHCOPh$
(ii) Benzyl (3R, 5R, E)-2-(2-benzamidoethylidene)-clavam-3-carboxylate
(a) N-Benzoyl benzyl carbamate

A suspension of benzoyl isocyanate (1.5 g, 0.0102mol) in dry benzene (8ml) was treated with a solution of benzyl alcohol (1.1 g, 0.0102mol) in benzene (5ml) and the reaction mixture was heated at 80°C for 30 minutes. After cooling the product was filtered from hexane as a colourless solid (1.45 g, 57%) m.p.118-120°C.

(b) A solution of benzyl clavulanate (2.19 g, 0.00757mol) in distilled THF (40ml) was treated with triphenylphosphine (2.28 g, 0.0087mol), N-benzoyl benzyl carbamate (3.38 g, 0.0132mol) and a solution of diethylazodicarboxylate (1.5 g, 0.00861mol) in THF (10ml) was added over 1 minute. After stirring at room temperature for 24 hours the reaction mixture was evaporated to a yellow oil which was purified by repeat column chromatography

on silica gel using 3:1 hexane/ethyl acetate as the eluting solvents, yielding a yellow oil (1.21 g). This oil was hydrogenated in dry THF (30ml) over 10% palladium on carbon (0.5 g) for 60 minutes at 25°C at 40psi. The reaction mixture was filtered and treated with a solution of sodium bicarbonate (0.14 g, 0.000167mol) in water (40ml) and the mixture freeze dried to give a brown solid which was dissolved in DMF (35ml) and treated with benzyl bromide (1 g, 0.00585mol). After stirring at room temperature for 6 hours the reaction mixture was evaporated to an oil, mixed with diethyl ether, filtered and the filtrate was washed with brine, dried ($MgSO_4$), evaporated to a brown oil which was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluting solvents. Recrystallisation of the appropriate fractions from ethyl acetate/hexane gave the products:

(i) colourless solid (0.104 g, 12.5%) m.p.143-144°C

Found: C, 67.4; H, 5.3; N, 7.2%

$C_{22}H_{20}N_2O_5$ requires: C, 67.3; H, 5.1; N, 7.1%

(ii) colourless solid (0.019g, 2.4 %) m.p. 160-162°C

Found: C, 67.5; H, 5.3; N, 7.2%

$C_{22}H_{20}N_2O_5$ requires: C, 67.3; H, 5.1; N, 7.1%

Example 112: $R^2 = O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = NHCOPh

6-(4-n-Butylphenyl)hexyl (3R, 5R, Z)-2-(2-benzamidoethylidene)-clavam-3-carboxylate,

Yield = 37%, colourless solid, m.p. 87-89°C, prepared as described in Example 111 above.

Found: C, 71.5; H, 7.2; N, 5.4%

$C_{31}H_{38}N_2O_5$ requires: C, 71.8; H, 7.4; N, 5.4%

Example 113: $R^2 = NH(CH_2)_6Ph$, $R^1 = NHCOCH_3$

N-6-Phenylhexyl-2-(2-acetamidoethylidene)-clavam-3-carboxamide

Benzyl (3R, 5R, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate (0.38 g, 0.00115mol) in dry THF (20ml) was hydogenated over 10% palladium on carbon (0.15 g) for minutes at 25°C at 20psi. The reaction mixture was filtered and the catalyst was washed with THF (30ml) and CH_2Cl_2 (30ml). The combined filtrates and solutions of DCC (0.20 g,0.00097mol) in dry CH_2Cl_2 (20ml) and 6-phenylhexylamine (0.165 g, 0.000931mol) in dry CH_2Cl_2 (20ml) were mixed together quickly. The reaction mixture was evaporated to near dryness and CH_2Cl_2 (20ml) was added. After stirring at room temperature for 1.5 hours the reaction mixture was cooled, filtered and the filtrate was evaporated to an oil which was purified by column chromatography on silica gel using ethyl acetate/ethanol as the eluting solvents and recrystallisation from ethyl acetate/pet ether, yielding the product as a colourless solid (0.102 g, 28%)

m.p.145-146°C.

Found: C, 66.1; H, 7.1; N, 10.6%

$C_{22}H_{29}N_3O_4$ requires: C, 66.1; H, 7.3; N, 10.5%

Example 114: R^2 = $NHO(CH_2)_5Ph$, $NHCOCH_3$

N-5-Phenylpentyloxy-2-(2-acetamidoethylidene)-clavam-3-carboxamide

2-(2-acetamidoethylidene)-clavam-3-carboxylic acid (derived from benzyl (3R, 5R, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate (0.7 g) as described in Example 113a) was treated with DCC (0.43 g) and 5-phenylpentyloxyamine (0.34 g) as described in Example 113a to give the product as a colourless solid (0.217 g, 29%) m.p. 126-129°C.

Found: C, 63.0; H, 6.7; N, 10.5%

$C_{21}H_{27}N_3O_5$ requires: C, 62.8; H, 6.8: N,10.5%

Example 115: R^2 = OCH_2-(2,4-diCl)Ph, R^1 = $NHCOCH_2NHCOCH_3$

2,4-Dichlorobenzyl (3R, 5R)-9-deoxy-9-(2-N-acetylglycinamido)clavulanate

Sodium (3R, 5R) 9-deoxy -9-(2-N-acetylgycinamido)clavulanate (0.125 g, 0.000391mol) and 2,4-dichlorobenzyl bromide (0.282 g, 0.001175mol) were stirred together in DMF (7.5ml) for 18 hours. The reaction was evaporated to dryness and the residue was partitioned between ethyl acetate (50ml) and water (25ml) and filtered to remove solid. The organic layer was dried ($MgSO_4$), combined with the solid and evaporated in vacuo to give a solid which was washed with diethyl ether and recrystallised from ethyl acetate to give the product as colourless solid (0.09 g, 50%) m.p. 180-181°C.

Found: C, 49.9; H, 4.3; N, 9.1%

$C_{19}H_{19}Cl_2N_3O_6$ requires: C, 50.0; H, 4.2; N, 9.2%

Example 116: R^2 = OCH_2-(2,4-diCl)Ph, R^1 = $NHCOCH_2NHCOCH_3$

2,4-Dichlorobenzyl (3S, 5S)-9-deoxy-9-(2-N-acetylglycinamido)clavulanate

Sodium (3S, 5S)-9-deoxy-9-(2-N-acetylglycinamido)clavulanate (0.135 g, 0.0042mol) and (0.30 g, 0.00125mol) were stirred together in DMF (7.5ml) for 21 hours. The reaction mixture was evaporated to an orange oil which was partitioned between ethyl acetate (75ml) and water (30ml). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to a clourless solid which was washed with diethyl ether to remove 2,4-dichlorobenzyl bromide. The residue was recrystallised from ethyl acetate to give the product as a colourless solid (0.097 g, 50%) m.p. 183-184 °C.

Found: C, 50.0; H, 4.0; N, 9.4%

$C_{19}H_{19}Cl_2N_3O_6$ requires: C, 50.0; H, 4.2; N, 9.2%

Example 117: R^2 = OCH_2Ph, R^1 = $NHCOCH_3$

Benzyl (3S, 5S, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate

(a) Benzyl (3S, 5S)-9-deoxy-9-(2-N-acetylglycinamido)clavulanate

Sodium (3S, 5S)-9-deoxy-9-(2-N-acetylglycinamido)clavulanate (125 g, 0.033mol) and benzyl bromide (50ml, 0.42mol) were stirred together in DMF (1.1l) for 24 hours. Ethy acetate (1.1l) was added and the reaction mixture was filtered and evaporated in vacuo to a brown oil which was purified by column chromatography on silica gel using chloroform/ethanol as the eluting solvents. Recrystallisation from ethyl acetate/ether gave the product as a light brown solid (12.9 g, 25%) m.p. 138-140°C.

(b) Benzyl (3S, 5S, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate

A solution of benzyl (3S, 5S)-9-deoxy-9-(2-N-acetylglycinamido)-clavulanate (0.48 g, 1.25mmol) in CH_2Cl_2 (25ml), cooled to -5°C, was treated with a solution of pyridine (0.99 g, 12.5mmol) in CH_2Cl_2 (2ml) folowed by thionyl chloride (0.59 g, 5mmol) in CH_2Cl_2 (2ml). The reaction mixture was stirred at 5°C for 10 minutes and at room temperature for 50 minutes, cooled to 5°C and treated with 2-aminothiophenol (1.25 g, 10mmol) in CH_2Cl_2 (2ml) and stirred at 5°C for 1 hour. Pyridine (1.98 g, 25mmol) and acetyl chloride (1.57 g, 20mmol) were added to the reaction mixture and it was stirred at room temperature for 1 hour. The reaction mixture was diluted with CH_2Cl_2 (25ml) and washed with 0.5M HCl, water, sat.$NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to a red tar which was purified by column chromatography on silica gel eluting with ethyl aceate and then 20:1 $CHCl_3$/methanol to give an orange oil. Trituration with diethyl ether yielded the product as a light brown solid (0.033 g, 8%) m.p. 129-132°C.

Found: C, 61.1; H, 5.5; N, 8.5%

$C_{17}H_{18}N_2O_5$(0.026EtOAc, 0.17$H_2$0) requires: C, 61.2; H, 5.6; N, 8.3%

Example 118: $R^2 = O(CH_2)_6$-(4-C_4H_9)Ph, $R^1 = NHCOCH_3$

6-(4-n-Butylphenyl)hexyl (3S, 5S, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate

and **Example 119**: $R^2 = O(CH_2)_6$-(4-C_4H_9)Ph, $R^1 = NHCOCH_3$

6-(4-n-Butylphenyl)hexyl (3S, 5S)-2-(2-acetamidoethyl)-clavam-3-carboxylate

Benzyl (3S, 5S, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate (0.21 g, 0.636mmol) in THF (20ml) was hydrogenated over 10% palladium on carbon (0.63 g) for 1.5 hours. The reaction mixture was filtered to remove catalyst and treated with a solution of $NaHCO_3$ (54mg, 0.643mmol) in water (5ml). The THF was removed in vacuo and the remaining solution was freeze dried to give an oil which was dissolved in DMF (15ml) and treated with 6-(4-n-butylphenyl)hexyl bromide (0.4 g, 1.35mmol) and the reaction mixture was stirred at room temperature for 20 hours and evaporated to an oil. This oil was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluting solvents and evaporation of the appropriate fractions gave the

products

(i) as a brown oil (0.005g, 1.7%).

^{1}H NMR-($CDCl_3$) δ 0.92 (t, J=7.3Hz, 3H, CH_3), δ 1.37 (m, 6H, CH_2), δ 1.59 (m, H, CH_2), δ 1.96 (s, 3H, $COCH_3$), δ 2.57 (t, J=7.6Hz, 4H, CH_2), δ (3.08 (d, J=15Hz, 1H, 6β-H), δ 3.50 (dd, J=2,15Hz, 1H, 6α-H), δ 3.94 (t, J=6.8Hz, 2H, 9,9'-H), δ 4.16 (m, 1H, $COCH_2$), δ 4.75 (t, J=7Hz, 1H, 8-H), δ 5.01 (s, 1H, 3-H), δ 5.52 (m, 1H, NH), δ 5.79 (d, J=2Hz, 1H, 5-H), δ 7.09 (s, 4H, Ar-H)

(ii) as a colourless oil (0.079 g, 27%)

^{1}H NMR-($CDCl_3$) δ 0.90 (t, J=7.3Hz, 3H, CH_3), δ 1.36 (m, 6H, CH_2), δ 1.56 (m, 6H, CH_2), δ 1.88 (m, 1H, 8'-H), δ 1.97 (s, 3H, $COCH_3$), δ 2.06 (m, 1H, 8-H), δ 2.57 (t, J=7.6Hz, 4H, CH_2), δ 2.92 (dd, J=4,12.6Hz, 1H, 6β-H), δ 3.40 (m, 3H, 6α-H, 9,9'-H), δ 4.13 (m, 3-H, CO_2CH_3), δ 4.33 (m, 1H, 2-H), δ 4.64 (d, J=6.4Hz, 3-H), δ 5.31 (d, J=4Hz, 5-H), δ 5.55 (d, J=2.4Hz, 5-H), δ 5.79 (m, 1H, NH), δ 7.09 (s, 4H, Ar-H)

Example 120: $R^2 = OCH_2Ph$, $R^1 = NHCOCH_2NHCOCH_3$

Benzyl (3R, 5R)-9-deoxy-9-(2-N-acetylglycinamido)clavulanate

Example 121: $R^2 = OCH_2Ph$, $R^1 = NHCOCH_2NHCOCH_3$

Benzyl (3S, 5S)-9-deoxy-9-(2-N-acetylglycinamido)clavulanate

Example 122: $R^2 = OCH_2Ph$, $R^1 = NHCO_2CH_2Ph$

Benzyl 9-N-benzyloxycarbonylamino deoxyclavulanate

Example 123: $R^2 = OCH_2$-(4-Br)Ph, $R^1 = NHCOCH_3$

4-Bromobenzyl (2S, 5S, Z)-2-(2-acetamidoethylidene)-clavam-3-carboxylate

Example 124: $R^2 = OCH_2Ph$, $R^1 = O(CH_2)_2OH$

Benzyl O-(2'-hydroxyethyl)clavulanate

Example 125: $R^2 = OCH_2Ph$, $R^1 = N_3$

Benzyl (3R, 5R, Z)-2-(2-azidoethylidene)clavam-3-carboxylate

Example 126: $R^2 = OCH_2Ph$, $R^1 = O(CH_2)_5CH_3$

Benzyl O-n-hexylclavulanate, Yield = 11.5%, yellow oil.

A solution of benzyl clavulanate (0.58 g, 0.002mol) in dry CH_2Cl_2 (30ml) was treated with hexyl iodide (0.428 g, 0.003mol), silver(I)oxide (0.47 g, 0.002mol) and powdered 4A° molecular sieves (2.2 g). The reaction mixture was stirred in the dark for 19 hours, filtered, evaporated in vacuo and the residue was purified by column chromatography on silica gel, yielding the product as a yellow oil (0.086 g, 11.5%).

Found: C, 67.5; H, 7.2; N, 4.0%

$C_{21}H_{27}NO_5$ requires: C, 67.5; H, 7.3; N, 3.8%

Example 127: $R^2 = OCH_2Ph$, $R^1 = OCH_3$

O-Methyl benzyl clavulanate. Yield = 42%, pale yellow oil.

Found: C, 63.8; H, 5.9; N, 4.7%

$C_{16}H_{17}NO_5$ requires: C, 63.4; H, 5.6; N, 4.6%

Example 128: $R^2 = OCH_2Ph$, $R^1 = OTHP$

Benzyl O-2-pyranosylclavulanate. Yield = 81%, colourless oil.

Found: C, 62.3; H, 6.2; N, 3.5%

$C_{20}H_{23}NO_6(0.17CH_2Cl_2)$ requires: C, 62.5; H, 6.1; N, 3.6%

Example 129: $R^2 = OCH_3$, $R^1 = OCH_3$

Methyl O-methylclavulanate

Example 130: $R^2 = OCH_2$-(4-NO_2)Ph, $R^1 = OTHP$

4-Nitrobenzyl O-tetrehydropyran-2'-yl)clavulanate

Example 131: $R^2 = OCH_2Ph$, $R^1 = OCH_2CO_2Et$

Benzyl O-(carboxymethyl)clavulanate. Yield = 4%, oil.

Found: C, 59.6; H, 5.6; N, 3.2%

$C_{19}H_{21}NO_7(0.1CH_2Cl_2)$ requires: C, 59.7; H, 5.6; N, 3.6%

Example 132: $R^2 = O(CH_2)_6$-(4-C_4H_9)Ph, $R^1 = SCH_3$

6-(4-Butylphenyl)hexyl (3R, 5R, Z)-2-methylthioethylidene-clavam-3-carboxylate

(a) 6-(4-n-Butylphenyl)hexyl bromide

6-Bromohexanoyl chloride (29.34 g, 0.14mol) in dry CH_2Cl_2 (30ml) was added over 5 minutes to a suspension of aluminium chloride (16.13 g, 0.12 mol) in CH_2Cl_2 (80ml) whilst keeping the temperature at 20-23°C. The mixture was stirred at room temperature for 30 minutes and treated with a solution of n-butylbenzene (14.9 g, 0.11 mol) in CH_2Cl_2 (30ml). After stirring at room temperature for 20 hours, triethylsilane (32 g, 0.28 mol) was added at 23-25°C over 10 minutes. The mixture was stirred at room temperature for 60 minutes then poured into ice water (200ml). The organic layer was separated, dried ($MgSO_4$) and evaporated in vacuo. The residue was distilled under reduced pressure to give a clear oil (28.35 g, 87%), boiling point 140-143°C/0.2mbar.

(b) 6-(4-n-Butylphenyl)hexyl clavulanate

A mixture of 6-(4-n-butylphenyl)hexyl bromide (7.48 g, 25mmol) and potassium clavulanate (5 g, 21mmol) in DMF (200ml) was stirred at room temperature for 20 hours. The mixture was evaporated to dryness and partitioned between ethyl acetate (200ml) and water (200ml).The organic layer was separated, washed with water, brine, dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography on silica gel using 2:1 pet ether/ethyl acetate as the eluting solvents, yielding the product as an orange oil (2.09 g, 24%).

(c) 6-(4-n-Butylphenyl)hexyl O-dichloroacetylclavulanate

6-(4-n-butylphenyl)hexyl clavulanate (1.88 g, 4.5mmol) was dissolved in dry dichloromethane (40ml), the solution was cooled to -30°C and treated with pyridine (0.44ml) and a solution of dichloroacetyl chloride (0.46ml) in CH_2Cl_2 (10ml) dropwise over 10 minutes. Stirring was continued at -30°C for 60 minutes, the reaction mixture was poured into 1N HCl (50ml), extracted with dichloromethane (25ml) and the combined organic layers washed with brine (x2),dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography on silica gel using 5:1 pet ether/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (1.24 g, 52%).

(d) 6-(4-n-Butylphenyl)hexyl (3R, 5R, Z)-2-methylthioethylidene clavam-3-carboxylate

A solution of 6-(4-n-butylphenyl)hexyl O-dichloroacetylclavulanate (1.59 g, 3mmol) in DMF (10ml) was cooled to -60°C and treated dropwise with a solution of sodium thiomethoxide (0.198 g, 3mmol) in DMF (30ml) over 10 minutes. The reaction mixture was stirred at -50°C for 30 minutes and at room temperature for 90 minutes. The reaction was cooled to -50°C and sodium thiomethoxide (0.065 g) was added, stirred at room temperature for 45 minutes, evaporated in vacuo to an orange oil which was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography on silica gel using 7:1 hexane/ethyl acetate as the eluting solvents, yielding the product as a yellow oil (0.41 g, 30%).

Found: C, 67.7; H, 8.0; N, 3.0%

$C_{25}H_{35}NO_4S$ requires: C, 67.4; H, 7.9; N, 3.1%

Example 133: $R^2 = O(CH_2)_6$-(4-C_4H_9)Ph, $R^1 = SOCH_3$

6-(4-n-Butylphenyl)hexyl (3R, 5R, Z)-2-methylsulphinylethylidene-clavam-3-carboxylate

6-(4-n-Butylphenyl)hexyl (3R,5R,Z)-2-methylthioethylidene clavam-3-carboxylate (0.32 g, 0.72mmol) was dissolved in CH_2Cl_2 (30ml) and cooled to -60°C and MCPBA (0.25 g, 0.72mmol) in CH_2Cl_2 (25ml) was added over 10 minutes. The reaction was stirred at -60°C for 30 minutes and allowed to warm to room temperature over 60 minutes. The reaction mixture was washed with aq Na_2SO_3, aq $NaHCO_3$, water, dried ($MgSO_4$), and evaporated to an oil which was purified by column chromatography on silica gel using ethyl acetate/ethanol as the eluting solvents, yielding the product as a colourless oil (0.13 g, 39%).

^{1}H NMR-($CDCl_3$) δ 0.92 (t, J=7.3Hz, 3H, CH_3), δ 1.35 (m, 6H, CH_2), δ 1.60 (m, 6H, CH_2), δ 2.51 (d, J=2.3Hz, 3H, $SOCH_3$), δ2.57 (t, J=7.5hZ, 4H, CH_2), δ 3.09 (d, J=17Hz, 1H, 6β-H), δ 3.51 (m, 3H, 9,9'-H, 6α-H), δ 4.17 (t, J=6.6Hz, 3H, CO_2CH_2), δ 4.80 (q, J=9.2, 11.1 Hz, 1H, 8-H), δ 5.12 (s, 1H, 3-H), δ 5.73 (dd, J=2.71Hz,1H, 5-H), δ 7.08 (s, 5H, Ar-H).

Example 134: $R^2 = O(CH_2)_6$-(4-C_4H_9)Ph. $R^1 = SO_2CH_3$
6-(4-n-Butylphenyl)hexyl (3R. 5R. Z)-2-methylsulphonylethylidene-clavam-3-carboxylate
6-(4-n-butylphenyl)hexyl (3R. 5R. Z)-2-methylthioethylidene clavam-3-carboxylate (0.2 g, 0.45mmol) was dissolved in CH_2Cl_2 (25ml) and cooled in an ice bath. A solution of mCPBA (0.62 g. 1.8mmol) in CH_2Cl_2 (25ml) was added over 10 minutes and the mixture stirred for 90 minutes in an ice bath. After warming to room temperature the mixture was washed with 5% Na_2SO_3, saturated $NaHCO_3$, water. dried ($MgSO_4$) and evaporated to a yellow oil. which was purified by column chromatography on silica gel using 3:2 pet ether/ethyl acetate as the eluting solvents. yielding the product as a colourless oil (0.11 g, 51%).
Found: C. 62.7; H, 7.3; N, 3.1%
$C_{25}H_{35}NO_6S$ requires: C. 62.9; H. 7.4; N. 2.9%
^{1}H NMR-($CDCl_3$) δ 0.92 (t. J=6.9 Hz. 3H. CH_3) , 1.40 (m, 4H. CH_2) . 1.6 (m. 8H. CH_2), 2.57 (t. J=6.7 Hz. 4H. CH_2-Ph) . 2.8 (s. 3H. SO_2CH_3) .3.1 (d. J=16.8Hz. 1H. 6β-H) . 3.5 (dd J=2.8.16.8Hz. 1H. 6α-H) . 3.8 (d. J=7.5Hz. 2H. CH_2 9.9'-H) .4.15 (t. J=3.8Hz. 2H OCH_2) . 4.85 (t, J=7.5Hz. 1H. 8-H) . 5.14 (s. 1H. 3-H) , 5.77 (d. J=2.8. 1H. 5-H) , 7.08 (bs. 4H. Ar-H)

The following compounds. Examples 135-137. were prepared as described above.

Example 135: $R^2 = O(CH_2)_6Ph$. $R^1 = SCH_3$
6-Phenylhexyl (3R. 5R. Z)-2-methylthioethylidene clavam-3-carboxylate.
Yield = 14%. yellow oil.
Found: C. 64.5; H. 7.0; N. 3.4%
$C_{21}H_{27}NO_4S$ requires: C. 64.8; H. 7.0; N. 3.6%

Example 136: $R^2 = O(CH_2)_6Ph$. $R^1 = SO_2CH_3$
6-Phenylhexyl (3R.5R.Z)-2-methylsulphonylethylidene clavam-3-carboxylate.
Yield = 68.7%. pale yellow oil.
Found: C. 59.3: H, 6.3: N. 3.0; S. 7.4%
$C_{21}H_{27}NO_6S(0.064CH_2Cl_2)$ requires: C. 59.3; H. 6.4; N. 3.3; S. 7.5%

Example 137: $R^2 = O(CH_2)_6$-(4-Br)Ph. $R^1 = SO_2CH_3$
6-(4-Bromophenyl)hexyl (3R. 5R. Z)-2-methylsulphonylethylidene clavam-3-carboxylate,
Yield = 37%. colourless oil.
^{1}H NMR-($CDCl_3$) δ 1.35 (m. 4H. CH_2) . 1.6 (m. 4H. CH_2) . 2.56 (t. J=7.5Hz. 2H. CH_2-Ph) . 2.82 (s. 3H. SCH_3) . 3.1 (d. J=16.8Hz. 1H. 6β-H) , 3.59 (dd. J=16.8. 2.75Hz. 1H. 6α-H) , 3.8 (d. J=8Hz. 2H. CH_2 9,9') , 4.17 (t, J=6.5Hz. 2H. CO_2CH_2) , 4.85 (t. J=8Hz. 1H, 8-H) . 5.14 (s. 1H. 3-H). 5.77 (d. J=2.75. 1H. 5-H) .7.06

(d, J=8.25Hz, 2H, Ar-H), 7.37 (d, J=8.25, 2H, Ar-H)

Example 138: $R^2 = OCH_2Ph$, $R^1 = SPh$

Benzyl (3R, 5R, Z)-2-phenylthioethylidene-clavam-3-carboxylate

Sodium hydride (0.08 g, 0.002mol) was suspended in dry DMF (10ml) and cooled in an ice bath. Thiophenol (0.21ml, 0.00205mol) was added over 2 minutes and the reaction was stirred at room temperature for 15 minutes and than cooled in an ice bath. Benzyl O-dichloroacetylclavulanate (0.8 g, 0.002mol) in DMF (5ml) was added and the reaction was stirred at room temperature for 1 hour and was then evaporated to a brown oil which was purified by column chromatography on silica gel using 3:1 hexane/ethyl acetate, yielding the product as a colourless oil (0.138 g, 18%).

Found: C, 66.0; H, 5.2; N, 3.3%

$C_{21}H_{19}NO_4S$ requires: C, 66.1; H, 5.0; N, 3.7%

Example 139: OCH_2-(2,4-diCl)Ph, $R^1 = SCH_2Ph$

2,4-Dichlorobenzyl (3R, 5R, Z)-2-benzylthioethylidene-clavam-3-carboxylate.

2,4-Dichlorobenzyl O-dichloroacetylclavulanate (2.35 g, 0.005mol) was dissolved in dry DMF (25ml) and benzyl mercaptan (0.93 g, 0.0075mol) was added. The mixture was cooled to -60°C and triethylamine (0.67ml, 0.0048mol) was added over 5 minutes. The reaction was stirred at -50 to -60°C for 60 minutes and then allowed to warm to room temperature, poured into diethyl ether (200ml) and washed with water (x3), brine, dried ($MgSO_4$) and evaporated to a yellow oil which was purified by column chromatography on silica gel using 5:1 hexane/ethyl acetate as the eluting solvents, yielding the product as a colourless oil. (1.53 g, 69%).

Found: C, 56.9; H, 4.2; N, 2.8; S, 7.0%

$C_{22}H_{19}Cl_2NO_4S$ requires: C, 56.9; H, 4.1; N, 3.0; S, 6.9%

Example 140: $R^2 = OCH_2$-(2,4-diCl)Ph, $R^1 = SOCH_2Ph$

2,4-Dichlorobenzyl (3R, 5R, Z)-2-benzylsulphinylethylidene-clavam-3-carboxylate.

2,4-Dichlorobenzyl (3R, 5R, Z)-2-benzylthioethylidene-clavam-3-carboxylate (Example 140) (0.695 g, 1.5mmol) was dissolved in CH_2Cl_2 (25ml) and cooled to -60°C. MCPBA (0.51 g, 1.5mmol) in CH_2Cl_2 (40ml) was added over 20 minutes and the suspension was stirred at -60°C for 1 hour and then allowed to warm to room temperature. The reaction was washed with dilute Na_2SO_3, $NaHCO_3$ (x2), water, brine, dried ($MgSO_4$) and evaporated to an oil which was purified by repeat column chromatography on silica gel using hexane/ethyl acetate as the eluting solvents, yielding the product as a colourless oil (0.225 g, 31%).

Found: C, 55.0, H, 4.5; N, 2.6; Cl, 13.5; S, 6.4%

$C_{22}H_{19}Cl_2NO_5S(0.42EtOAc)$ requires: C, 55.0; H, 4.4; N, 2.7; Cl, 13.7; S, 6.2%

Example 141: $R^2 = OCH_2$-(2,4-diCl)Ph, $R^1 = SO_2CH_2Ph$

2.4-Dichlorobenzyl (3R, 5R, Z)-2-benzylsulphonylethylidene-clavam-3-carboxylate.

2.4-Dichlorobenzyl (3R, 5R, Z)-2-benzylthioethylidene-clavam-3-carboxylate (Example 140) (0.35 g, 0.75mmol) was dissolved in CH_2Cl_2 (30ml) and cooled in an ice bath. MCPBA (1.04 g, 3mmol) in CH_2Cl_2 (25ml) was added over 10 minutes and the reaction was stirred in the ice bath for 90 minutes and was then allowed to warm to room temperature. The reaction was washed with dilute Na_2SO_3, $NaHCO_3$ (x2), water, dried ($MgSO_4$) and evaporated to an oil which was purified by column chromatography on silica gel using hexane/ethyl acetate as the eluting solvents, yielding the product as a colourless oil Recrystallisation from ethyl acetate gave the product as a colourless solid (0.15 g, 40%) m.p. 115-116°C.

Found: C, 53.1; H, 4.0; N, 2.9; Cl, 14.0; S, 6.7%

$C_{22}H_{19}Cl_2NO_6S$ requires: C, 53.2; H, 3.9; N, 2.8; Cl, 14.3; S, 6.5%

The following compounds, Examples 142-146 were prepared as described above in Examples 138-141.

Example 142: $R^2 = OCH_2Ph$, $R^1 = S(CH_2)_5CH3$

Benzyl (3R, 5R, Z)-2-hexylthioethylidene-clavam-3-carboxylate, Yield = 31%, colourless oil.

Found: C, 64.7; H, 6.8; N, 3.6; S, 8.0%

$C_{21}H_{27}NO_4S$ requires: C, 64.8; H, 7.0; N, 3.6; S, 8.2%.

Example 143: $R^2 = OCH_2Ph$, $R^1 = SO_2(CH_2)_5CH_3$

Benzyl (3R, 5R, Z)-2-hexylsulponylethylidene-clavam-3-carboxylate, Yield = 36%, colourless oil.

Found: C, 59.2; H, 6.3; N, 2.9; S, 7.9%

$C_{21}H_{27}NO_6S(0.03CH_2Cl_2)$ requires: C, 59.6; H, 6.4; N, 3.3; S, 7.6%

Example 144: $R^2 = OCH_2Ph$, $R^1 = SCH_2Ph$

Benzyl (3R, 5R, Z)-2-benzylthioethylidene-clavam-3-carboxylate, Yield = 29%, colourless oil.

Found: C, 66.7; H, 5.4; N, 3.4; S, 8.2%

$C_{22}H_{21}NO_4S$ requires: C, 66.8; H, 5.4; N, 3.5; S, 8.1%

Example 145: $R^2 = OCH_2Ph$, $R^1 = SOCH_2Ph$

Benzyl (3R, 5R, Z)-2-benzylsulpinylethylidene-clavam-3-carboxylate, Yield = 23%, colourless oil.

Found: C, 63.5; H, 5.4; N, 3.0%

$C_{22}H_{21}NO_5S(0.08EtOAc, 0.18H_2O)$ requires: C, 63.6; H, 5.3; N, 3.3%

Example 146: $R^2 = OCH_2Ph$, $R^1 = SO_2CH_2Ph$

Benzyl (3R, 5R, Z)-2-benzylsulponylethylidene-clavam-3-carboxylate. Yield = 68%, colourless oil.

Found: C, 60.7; H, 5.0; N, 3.2%

$C_{22}H_{21}NO_6S(0.05CH_2Cl_2, 0.24H_2O)$ requires: C, 60.7; H, 5.0; N, 3.2%

Example 147: $R^2 = O(CH_2)_6$-Ph, $R^1 = NHCOPh$

6-(phenyl)hexyl (3R, 5R, Z)-2-(2-benzoylaminoethylidene)clavam-3-carboxylate

and

Example 148: $R^2 = O(CH_2)_6$-Ph, $R^1 = NHCOPh$

6-(phenyl)hexyl (3R, 5R, E)-2-(2-benzoylaminoethylidene)clavam-3-carboxylate

a. 6-(phenyl)hexyl (3R, 5R, Z)-2-(2-azidoethylene)clavam-3-carboxylate

6-(phenyl)hexyl clavulanate (10 g) in didthyl ether (100 ml) was treated with pyridine and thionyl chloride at -60°C to -40°C for 0.3 h. After aqueous work-up the organic extracts were evaporated and the residue dissolved in acetone (100 ml) and treated with NaN_3 (1.07g) in water (10 ml) for 1h. After acidification, and washing of the organic solution with water the organic extracts were evaporated, and chromatographed to give 6-(phenyl)hexyl (3R, 5R, Z)-2-(2-azidoethylidene)clavam-3-carboxylate (0.96 g).

b. 6-(Phenyl)hexyl (3R, 5R, Z)-2-(2-azidoethylene)clavam-3-carboxylate (0.96 g)was dissolved in THF (30 ml) and treated with Zn dust (1.63 g) and 2N HCl, keeping the pH between 2.5 and 3. After stirring for 2h the mixture was neutralised, filtered and extracted with ethyl acetate. The organic extracts were washed with brine , dried and concentrated to 30 ml, cooled to -40 to -50C and treated with pyridine and benzoyl chloride. After aqueous work-up the organic extracts were evaporated and chromatographed to give the title compounds as cream solids.

(i) 6-(phenyl)hexyl (3R, 5R, Z)-2-(2-benzoylaminoethylidene)clavam-3-carboxylate, 0.56 g, m.p. 93-94°C

(i) 6-(phenyl)hexyl (3R, 5R, E)-2-(2-benzoylaminoethylidene)clavam-3-carboxylate, 0.05 g, m.p. 106-107°C

Example 149 $R^2 = O(CH_2)_6$-Ph, $R^1 = NHCOCH_3$

6-(Phenyl)hexyl (3S, 5S, Z)-2-(2-acetamidoethylene)clavam-3-carboxylate

a. 6-(Phenyl)hexyl (3S, 5S, Z)-2-(2-N-acetylglycinamidoethylene)clavam-3-carboxylate (4.6 g) was prepared from sodium (3S, 5S)-9-deoxy-9-(2-N-acetylglycinamido)clavulanate (40 g) and 6-phenylhexyliodide (16.8 g) by the method described in Example 116 and was isolated as a yellow solid.

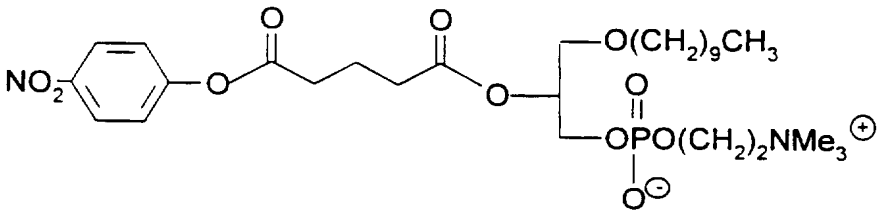
b. 6-(Phenyl)hexyl (3S, 5S, Z)-2-(2-N-acetylglycinamidoethylene)clavam-3-carboxylate (2.3 g) in dichloromethane (125 ml) at -10C was treated with pyridine (3.95 g) in

dichloromethane (10 ml) and thionyl chloride (2.38 g) in dichloromethane (10 ml), then the mixture stirred at room temperature for 1h. The mixture was cooled to -10C, and treated with 2-aminothiophenol (5 g), stirred for 1 h, and treated with pyridine (7.9 g) and acetyl chloride (6.3 g) in a total of 40 ml of dichloromethane. After stirring at room temperature for 1 h and aqueous work-up the title compound was isolated as a yellow semi-solid after chromatography (0.05 g)

DATA

1. Screen for Lp-PLA$_2$ inhibition.

Enzyme activity was determined by measuring the rate of turnover of the artificial substrate (A) at 37 °C in 50mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid) buffer containing 150mM NaCl, pH 7.4.



(A)

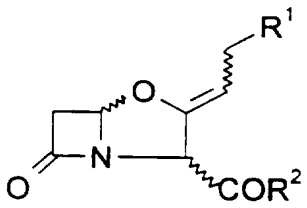
Assays were performed in 96 well titre plates.

Lp-PLA$_2$ was pre-incubated at 37 °C with vehicle or test compound for 10 min in a total volume of 180 µl. The reaction was then initiated by the addition of 20 µl 10x substrate (A) to give a final substrate concentration of 20 µM. The reaction was followed at 405 nm for 20 minutes using a plate reader with automatic mixing. The rate of reaction was measured as the rate of change of absorbance.

Results: The majority of compounds of Examples 1-149 had IC_{50}s in the range 0.002-50 µM with many (e.g. Examples 25-30, 55-57, 59-61, 64-77, 87-91, 99-102, 106-108) having IC_{50}s < 0.1 µM whilst Examples 53, 56, 71, 87, 88 and 137 have IC_{50}s < 0.01 µM.

Claims

1. A compound of structure (I):



(I)

in which:

R^1 is OH, $OCOR^3$ OCHO, $O(CH_2)_nOR^5$, OC_{1-12}alkyl, $O(CH_2)_nCO_2R^5$, $-S(O)_pC_{1-12}$alkyl, $S(CH_2)_q$Ph, $S(O)_r(CH_2)_n$Ph, N_3, NR^6R^7 or  ;

R^2 is $O(CH_2)_n$Ph in which the phenyl ring may optionally be substituted, $O(CH_2)_n$naphthyl, $O(CH_2)_nCOPh$, $O(CH_2)_nSPh$, $OCH(Ph)C_{1-6}$alkyl, OC_{1-6}alkyl, $NR^{10}(CH_2)_q$Ph, $NR^{10}(CH_2)_nCOPh$, $N(R^8)O(CH_2)_n$Ph;

R^3 is C_{1-12}alkyl, C_{2-12}alkenyl, optionally substituted phenyl, $CH(Ph)_2$, biphenyl, $(CH_2)_n$Ph, $(CH_2)_n$Het, $(CH_2)_nCO_2R^8$, $(CH_2)_nC_{3-6}$cycloalkyl, $C(R^9)_3$, adamantyl, naphthyl, C_{3-6}cyclohexyl, $(CH_2)_n$Ph$(CH_2)_n$Ph or PhOPh;

R^5 is hydrogen or C_{1-6}alkyl;

one of R^6 and R^7 is hydrogen or C_{1-6}alkyl, and the other is CHO, CH_2Ph, COC_{1-6}alkyl, COPh, $COCH_2NHCOC_{1-6}$alkyl or $NHCOOCH_2$Ph;

R^8 is hydrogen or C_{1-6}alkyl;

R^9 is hydrogen or halogen;

R^{10} is hydrogen, hydroxy, C_{1-6}alkyl or $OCOCH_3$;

m is 1 or 2; n is 1 to 8; p is 0, 1 or 2; q is 0 to 6 and r is 0, 1 or 2;

and salts, hydrates and solvates thereof.

2. A compound as claimed in claim 1 in which R^1 is OH, $OCOR^3$ or NR^6R^7.

3. A compound as claimed in claim 1 or 2 in which R^2 is $O(CH_2)_n$Ph, in which n is 1 to 8.

4. A compound as claimed in any one of claims 1 to 3 in which R^3 is C_{1-12}alkyl.

5. A compound as claimed in any one of claims 1 to 4 in which R^5 is hydrogen.

6. A compound as claimed in any one of claims 1 to 5 in which one of R^6 and R^7 is hydrogen and the other is COC_{1-6}alkyl.

7. A compound as claimed in any one of claims 1 to 6 in which R^8 is hydrogen.

8. A compound as claimed in any one of claims 1 to 7 in which one group R^9 is hydrogen and the other two are halogen, in particular chlorine.

9. A compound as claimed in any one of claims 1 to 8 in which R^{10} is hydrogen.

10. A compound as claimed in any one of claims 1 to 9 in which m is 2.

11. A compound as claimed in any one of claims 1 to 10 in which n is 6.

12. A compound as claimed in any one of claims 1 to 11 in which p is 2.

13. A compound as claimed in any one of claims 1 to 12 in which q is 0 to 6.

14. A compound as claimed in any one of claims 1 to 13 in which r is 0, 1 or 2.

15. A compound as claimed in claim 1 in which:
$R^2 = O(CH_2)_6$-(4- F)Ph. R^1 = OH:R^2 = OCH_3, R^1 = OH;
$R^2 = OC_6H_{13}$, R^1 = OH;
$R^2 = OC_{18}H_{37}$, R^1 = OH;
$R^2 = OCH_2$Ph. R^1 = OH;
$R^2 = OCH_2$-(4-NO_2)Ph. R^1 = OH;
$R^2 = OCH_2$-(4-Cl)Ph. R^1 = OH;
$R^2 = OCH_2$-(4-CH3)Ph. R^1 = OH;
$R^2 = OCH_2$-(4-Br)Ph. R^1 = OH;
$R^2 = OCH_2$-(4-OCH_3)Ph. R^1 = OH;
$R^2 = OCH_2$-(4-$(CH_3)_3$)Ph. R^1 = OH;
$R^2 = OCH_2$-(4-Ph)Ph. R^1 = OH;
$R^2 = OCH_2$ -1-Naphthyl. R^1 = OH;
$R^2 = OCH_2$-(4-OH. 3,5-di-tert-butyl)Ph. R^1 = OH;

R^2= OCH_2-(2,4-diCl)Ph, R^1 = OH;
R^2= OCH_2-(2,6-diCl)Ph, R^1 =OH;
R^2= OCH_2-(2,5-diCl)Ph, R^1 =OH;
R^2= OCH_2-(2,4-diCl)Ph, R^1 = OH;
R^2= $O(CH_2)_5CO$-(4-Cl)Ph, R^1 = OH;
R^2= $OCH(CH_3)$Ph, R^1 = OH;
R^2= $O(CH_2)_3$Ph, R^1 = OH;
R^2= $O(CH_2)_8$Ph, R^1 = OH;
R^2= $O(CH_2)_6$-(4-Br)Ph, R^1 = OH;
R^2= $O(CH_2)_6$Ph, R^1 = OH;
R^2= $O(CH_2)_6$-(4-Cl)Ph, R^1 = OH;
R^2= $O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = OH;
R^2= $O(CH_2)_6$-(2,4-diCl)Ph, R^1 = OH;
R^2= $O(CH_2)_6$-(2,4-diCH_3)Ph, R^1 = OH;
R^2= $O(CH_2)_5$-(2,4-diCl)Ph, R^1 = OH;
R^2= $O(CH_2)_4$-(4-CH_3)Ph, R^1 = OH;
R^2= $O(CH_2)_4$-(4-OCH_3)Ph, R^1 = OH;
R^2= $O(CH_2)_4$-(4-Ph)Ph, R^1 = OH;
R^2= $O(CH_2)_6$-(4-OH)Ph, R^1 = OH;
R^2= $O(CH_2)_6$-(4-OCH_3)Ph, R^1 = OH;
R^2= $O(CH_2)_6$S-(4-OH)Ph, R^1 = OH;
R^2= $O(CH_2)_5$S-(4-OH,3,5-di-tert-butyl)Ph, R^1 = OH;
R^2= $O(CH_2)_5$SPh, R^1 = OH;
R^2= $OCH(C_5H_{11})$Ph, R^1 = OH;
R^2= $NH(CH_2)_6$Ph, R^1 = OH;
R^2= $NH(CH_2)_6$-(4-F)Ph, R^1 = OH;
R^2= $N(CH_3)(CH_2)_6$-(4-F)Ph, R^1 = OH;
R^2= $N(CH_3)(CH_2)_6$- (4-C_4H_9)Ph, R^1 = OH;
R^2= $N(CH_3)CH_2$Ph, R^1 = OH;
R^2= $NH(CH_2)_4$Ph, R^1 = OH;
R^2= $NHCH_2$Ph, R^1 = OH;
R^2= $NHO(CH_2)_6$-(4-C_4H_9)Ph, R^1 = OH;
R^2= $NHOCH_2$Ph, R^1 = OH;
R^2= $NHO(CH_2)_5$Ph, R^1 = OH;
R^2= NH-(4-CH_3)Ph, R^1 = OH;

R^2= $NHCH_2COPh$, R^1 = OH;
R^2= OCH_3, R^1 = OH;
R^2= $O(CH_2)_6Ph$, R^1 = $OCOCH_3$;
R^2= OCH_2-(4-NO_2)Ph, R^1 = OCO-(4-Ph)Ph;
R^2= $O(CH_2)_6$-(4-Br)Ph, R^1 = $OCOCH_3$;
R^2= $O(CH_2)_6$-(4-Br)Ph, R^1 = OCO-(4-Ph)Ph;
R^2= $O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = $OCOCH_3$;
R^2= $O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = OCOPh;
R^2= $O(CH_2)_6$-(4-Cl)Ph, R^1 = $OCOCH_3$;
R^2= OCH_2-(2,4-diCl)Ph, R^1 = OCOPh;
R^2= OCH_2-(2,4-diCl)Ph, R^1= $OCOCH_3$;
R^2= OCH_2Ph, R^1 = $OCOCH_3$;
R^2= OCH_2Ph, R^1 = OCO-(4-Ph)Ph;
R= OCH_2Ph, R^1 = OCOPh;
R^2= OCH_2Ph, R^1 = $OCO(CH_2)_2Ph$;
R^2= OCH_2Ph, R^1 = $OCOCH_2Ph$;
R^2= OCH_2Ph, R^1 = $OCO(CH_2)_4CH_3$;
R^2= OCH_2Ph, R^1 = $OCO(CH_2)_8CH=CH_2$;
R^2= OCH_2Ph, R^1 = OCO-(1-adamantyl);
R^2= OCH_2Ph, R^1 = $OCOCH_2$-(2-thienyl);
R^2= OCH_2Ph, R^1 = $OCO(CH_2)_2CO_2Et$;
R= OCH_2Ph, R^1 = OCO-(4-CN)Ph;
R^2= OCH_2Ph, R^1 = OCO-(4-NO_2)Ph;
R^2= OCH_2Ph, R^1 = $OCOCH(Ph)_2$;
R^2= OCH_2Ph, R^1 = $OCO(CH_2)_7CH_3$;
R^2= OCH_2Ph, R^1 = $OCO(CH_2)_2$-C_5H_9;
R^2= OCH_2Ph, R^1 = OCO-$(CH_2)_5Ph$;
R^2= OCH_2Ph, R^1 = OCO-(1-naphthyl);
R^2= OCH_2Ph, R^1 = $OCOC_6H_{11}$;
R^2= OCH_2Ph, R^1 = OCO(4-CH_2Ph)Ph;
R^2= OCH_2Ph, R^1 = OCO(4-O-Ph)Ph;
R^2= $NH(CH_2)_6Ph$, R^1 = $OCOCH_3$;
R^2= $(CH_2)_6$-(4-OCH_3)Ph, R^1 = $OCOCH_3$;
R^2= $NHO(CH_2)_5Ph$, R^1 = $OCOCH_3$;
R^2= $NH(CH_2)_6$-(4-F)Ph, R^1 = $OCOCH_3$;
R^2= $N(CH_3)(CH_2)_6$-(4-F)Ph, R^1 = $OCOCH_3$;

R^2= $O(CH_2)_5CO$-(4-Cl)Ph, R^1 = $OCOCH_3$;
R^2= $O(CH_2)_6$-(4-F)Ph, R^1 = $OCOCH_3$;
R^2= $O(CH_2)_6$-(4-Cl)Ph, R^1 = $OCOCHCl_2$;
R^2= OCH_2-(3,4-diCl)Ph, R^1 = OCOPh;
R^2= OCH_2-(3,4-diCl)Ph, R^1 = $OCOCH_3$;
R^2= $N(CH_3)(CH_2)_6$-(4-C_4H_9)Ph, R^1 = OCOPh;
R^2= $NHO(CH_2)_6$-(4-C_4H_9)Ph, R^1 = $OCOCH_3$;
R^2= $N(CH_3)(CH_2)_6$-(4-C_4H_9)Ph, R^1 = $OCOCH_3$;
R^2= OCH_2Ph, R^1 = $OCOCHCl_2$;
R^2= $N(OH)(CH_2)_6$-(4-F)Ph, R^1 = $OCOCH_3$;
R^2= $N(OCOCH_3)(CH_2)_6$-(4-F)Ph, R^1 = $OCOCH_3$;
R^2= $N(OCOCH_3)(CH_2)_6$-(4-C_4H_9)Ph, R^1 = $OCOCH_3$;
R^2= $NHO(CH_2)_6Ph$, R^1 = $OCOCH_3$;
R^2= $O(CH_2)_6$-(4-F)Ph, R^1= OCHO;
R^2 = $O(CH_2)_6Ph$, R^1 = $N(CH_3)CH_2Ph$;
R^2 = $O(CH_2)_6$-(4-F)Ph, R^1 = NHCHO;
R^2 = $O(CH_2)_6Ph$, R^1 = NHCHO;
R^2 = $O(CH_2)_6Ph$, R^1 = $NHCOCH_3$;
R^2 = $O(CH_2)_6$-(4-F)Ph, R^1 = $NHCOCH_3$;
R^2 = $O(CH_2)_6$-(4-Cl)Ph, R^1 = $NHCOCH_3$;
R^2 = $O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = $NHCOCH_3$;
R^2 = OCH_2Ph, R^1 = $NHCOCH_3$;
R^2 = OCH_2Ph, R^1 = NHCOPh;
R^2 = OCH_2Ph, R^1 = NHCOPh;
R^2 = $O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = NHCOPh;
R^2 = $NH(CH_2)_6Ph$, R^1 = $NHCOCH_3$;
R^2 = $NHO(CH_2)_5Ph$, $NHCOCH_3$;
R^2 = OCH_2-(2,4-diCl)Ph, R^1 = $NHCOCH_2NHCOCH_3$;
R^2 = OCH_2-(2,4-diCl)Ph, R^1 = $NHCOCH_2NHCOCH_3$;
R^2 = OCH_2Ph, R^1 = $NHCOCH_3$;
R^2 = $O(CH_2)_6$-(4-C_4H_9)Ph, R^1 = $NHCOCH_3$;
R^2 = OCH_2Ph, R^1 = $NHCOCH_2NHCOCH_3$;
R^2 = OCH_2Ph, R^1 = $NHCOCH_2NHCOCH_3$;
R^2 = OCH_2Ph, R^1 = $NHCO_2CH_2Ph$;
R^2 = OCH_2-(4-Br)Ph, R^1 = $NHCOCH_3$;
R^2 = OCH_2Ph, R^1 = $O(CH_2)_2OH$;

$R^2 = OCH_2Ph$, $R^1 = N_3$;
$R^2 = OCH_2Ph$, $R^1 = O(CH_2)_5CH_3$;
$R^2 = OCH_2Ph$, $R^1 = OCH_3$;
$R^2 = OCH_2Ph$, $R^1 = OTHP$;
$R^2 = OCH_3$, $R^1 = OCH_3$;
$R^2 = OCH_2$-(4-NO_2)Ph, $R^1 = OTHP$;
$R^2 = OCH_2Ph$, $R^1 = OCH_2CO_2Et$;
$R^2 = O(CH_2)_6$-(4-C_4H_9)Ph, $R^1 = SCH_3$;
$R^2 = O(CH_2)_6$-(4-C_4H_9)Ph, $R^1 = SOCH_3$;
$R^2 = O(CH_2)_6$-(4-C_4H_9)Ph, $R^1 = SO_2CH_3$;
$R^2 = O(CH_2)_6Ph$, $R^1 = SCH_3$;
$R^2 = O(CH_2)_6Ph$, $R^1 = SO_2CH_3$;
$R^2 = O(CH_2)_6$-(4-Br)Ph, $R^1 = SO_2CH_3$;
$R^2 = OCH_2Ph$, $R^1 = SPh$;
OCH_2-(2,4-diCl)Ph, $R^1 = SCH_2Ph$;
$R^2 = OCH_2$-(2,4-diCl)Ph, $R^1 = SOCH_2Ph$;
$R^2 = OCH_2$-(2,4-diCl)Ph, $R^1 = SO_2CH_2Ph$;
$R^2 = OCH_2Ph$, $R^1 = S(CH_2)_5CH3$;
$R^2 = OCH_2Ph$, $R^1 = SO_2(CH_2)_5CH_3$;
$R^2 = OCH_2Ph$, $R^1 = SCH_2Ph$;
$R^2 = OCH_2Ph$, $R^1 = SOCH_2Ph$;
$R^2 = OCH_2Ph$, $R^1 = SO_2CH_2Ph$;
$R^2 = O(CH_2)_6$-Ph, $R^1 = NHCOPh$; and
$R^2 = O(CH_2)_6$-Ph, $R^1 = NHCOCH_3$

16. A pharmaceutical composition comprising a compound according to any one of the preceding claims and a pharmaceutically acceptable carrier.

17. A compound according to claim 1 for use in therapy.

18. The use of a compound of structure (I) as defined in claim 1 in the manufacture of a medicament for treating as defined in claim 1 in the manufacture of a medicament for treating atherosclerosis.

19. The use of a compound of structure (I) as defined in claim 1 in the manufacture of a medicament for treating diabetes, hypertension, angina pectoris, after ischaemia.

reperfusion, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation, inflammatory conditions of the brain such as Alzheimer's Disease, neuropsychiatric disorders such as schizophrenia, and psoriasis.

INTERNATIONAL SEARCH REPORT

Intern :l Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D503/16 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	GB 2 017 099 A (GLAXO GROUP LIMITED) 3 October 1979 see the whole document ---	1-17
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1996	20.12.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Chouly, J

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